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VOL 2 NO 5 **DANISH MEDICAL BULLETIN** SEPT. 1955

TREATMENT OF LUPUS VULGARIS WITH CALCIFEROL ALONE

RESULTS AFTER FIVE YEARS OF OBSERVATION

By POUL V. MARCUSSEN

The influence of calciferol on lupus vulgaris seems to be an inhibition of the lupous tissue, causing the tubercle bacilli to be liberated without their virulence being influenced. It is still uncertain whether calciferol acts by specific tissue damage or by inhibiting the allergic properties of the tubercle bacillus. The latter possibility seems the more likely (van der Lugt (9)). Lupus of the skin is, as might be expected, fairly resistant to streptomycin, because the tubercle bacilli of decreased virulence are found intracellularly. Isonicotinic acid hydrazide has a pronounced preliminary effect. This effect also seems limited, not as a consequence of the development of resistance, but presumably because the phagocytized tubercle bacilli in some cases are resting forms (8), dividing too rarely to be in the susceptible phase within a reasonable period of treatment. It will therefore possibly be necessary to continue with calciferol, which liberates the lupus bacilli from the cells, to allow effective treatment with chemotherapeutic agents. A survey of the final results of calciferol on a series of cases submitted to no other treatment is necessary as a basis for evaluation of such a combined treatment.

PREVIOUS INVESTIGATIONS

Most investigations from recent years show the difficulty of keeping a large series of patients under regular control for a number of years. Leaving out of account the very few series that showed an exceptionally high or an exceptionally low cure rate (3, 7), the frequency of primary freedom from symptoms was from 32 to 68 % in the larger series reported (Table 1). In the papers stating the frequency of relapse it is seen that only about half of the patients could be followed up and that the observation period rarely exceeded an average of 2 years. Pogorzelski and Miedzinski (14) emphasize that the observation period ought to be not less than 3 years, and Schreus (17) even wants 5 years. Meyer, Gaulier, and Desgrez (12) and Miescher (13) have pointed out the high incidence of relapse. This ranged from 42 to 53.5 % in the stated reports. Frühwald (4), however, found relapse in only 9 %, but also a low incidence of primary freedom from symptoms (46 %), while Pogorzelski and Miedzinski found relapse in 15.6 %, but likewise a low primary cure rate (54 %). Owing to the great loss of patients, the total result of the treatment is shown most plainly in Pogorzelski and Miedzinski's paper (15). These workers found a 6-year cure rate of 38.4 %.

MATERIAL AND PROCEDURE

From 1946-8 to 1955 a series of 284 consecutive cases were submitted to systematic treatment and control examinations. The treatment was given on the lines suggested by Sonne (18), i. e. an initial dose of 4.5 mg daily, followed by a dose varying according to the patient's tolerance. The treatment was, as far as possible, continued until there had been clinically and pathologically verified freedom from symptoms for at least 12 months, or until a total dose of not less than 1 g calciferol had been administered.

From 1950 the result of the treatment was controlled bacteriologically, and the patients were examined systematically for tuberculosis in other organs. Control examinations were, where possible, carried out 3 and 6 months after the conclusion of the treatment, and then at intervals of 12 months. If relapse was ascertained, another

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Table 1.

Authors	Year	Number of pts.	Symptom free	Followed up	Observation period	Relapses	Finally cured
Meyer, Gaulier and Desgrez	1946	301	38 %	148	2 years	45 %	
Miescher	1949	89	68 %		2 years	53.5 %	
Ruiter and Groen	1950	100	32 %				
Carpentier	1951	106	64 %	58	4 years	50 %	
Huriez	1952	150	2/3			1.2	
Review of 22 series af cases (Huriez)	1952	194	1028			440	
Braun	1952	77	60 %	39	6-26 mos.	50 %	
Frühwald	1953	100	46 %	46	2 mos.-4 years	9 %	
Pogorzelski and Miedzinski	1953	784	54 %		6 years	15.6 %	38.4 %
van der Lugt	1954	216	104				

treatment was instituted. Some of the patients were thus given up to four treatments, while others changed to other forms of treatment. Owing to the difficulty of having a large group of patients under regular observation, 14 patients living abroad were ruled out in 1950. Six patients, whose diagnosis was uncertain, were likewise ruled out. The series of patients was thereafter supplemented by consecutive numbers. A detailed account of the preliminary results has been given in various publications (Sonne (18), Marcussen and Nielsen (11), Marcussen (10)). Final control examinations were made in 1955. To facilitate comparison with other series of cases the most important results are rendered graphically.

THE PRIMARY RESULTS OF TREATMENT

The results of the 410 series of treatment are set out in Table 2. It is seen that 78.5 % obtained freedom from symptoms after one treatment, whereas 16.5 % did not. 5 % died or lapsed from treatment. The result of the second treatment was considerably less favourable: only 45.5 % symptom-free. After the third treatment only 30.4 % were symptom-free.

LATE RESULTS

It is intended to follow the total number of symptom-free (223 patients) through 10 years from the cessation of treatment, or until they must be dropped on account of relapse or from other causes, to which we have so far reckoned only death, emigration, or interfering treatment (plastic surgery). The Danish Tuberculosis Act, which gives access to free treatment and free conveyance, if necessary, as well as a grant from the Finsen Institute, which has enabled the author to undertake an annual journey with consultations in 20 to 30 Danish towns, has made it possible to carry through the observations without definitive loss of patients from other

Table 2.

Survey of results of 410 courses of treatment with calciferol in total doses varying about 1 g to 284 patients with lupus vulgaris controlled from 1946—8 to 1955.

Series of treatments	1	2	3	4
Number of patients	284	101	23	2
Dead during treatment	(8)	0	0	0
Treatment interrupted by patient	4	3	0	0
Treatment not yet concluded	1	2	2	0
Treatment carried through and concluded	271	96	21	2
Symptom-free at conclusion of treatment	223 (78.5 %)	46 (45.5 %)	7 (30.4 %)	1
Not cured	48 (16.5 %)	50 (54.5 %)	14 (69.6 %)	1
(Dead among not cured)	(3)			
Relapse at conclusion of observation (1955)	120 (42.3 %)	36 (35.6 %)	5 (21.7 %)	0
Symptom-free — —	83 (29.2 %)	9 (8.9 %)	2 (8.7 %)	1
Dead (as symptom-free) — —	15	1	0	0
Lost (as symptom-free) — —	5	0	0	0
(Dead after relapse)	(6)			
Death total	32	1	0	0

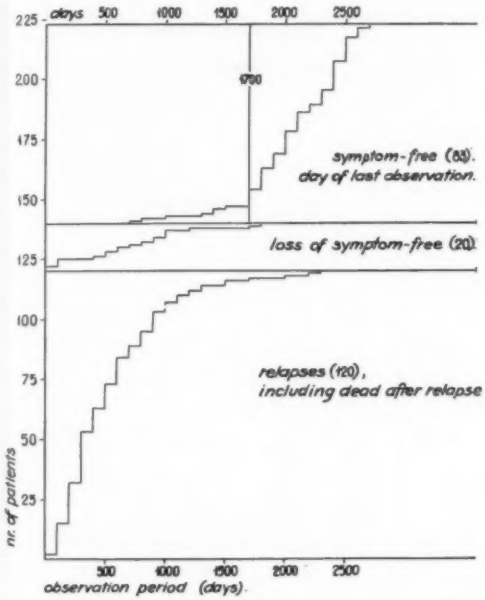

Fig. 1.

Observation of 223 primarily symptom-free patients show how the series of patients is reduced by loss and relapse. Further, it shows the day of the last examination of the still symptom-free patients.

causes than those mentioned. Owing to the varying dates for the institution of treatment and the great variations in the period of treatment, the observation period for the total series is as yet relatively short. However, it was necessary, as a basis for comparison with other methods of treatment, to form an estimate of the final results so far.

Fig. 1 shows the results of observation of the 223 patients who became symptom-free after the first treatment. The percentage values were calculated on the basis of the original number of patients (284).

It is seen that 20 patients (7 %) have been lost. Of these 15 died, while 4 emigrated, and one was submitted to plastic reconstruction (after 1106 days of observation). All these patients were symptom-free by the time they passed out of the investigation.

120 patients (42.3 %) relapsed. The majority relapsed after 100 and before 1000 days of observation. On account of the varying lengths of the observation periods, definite conclusions regarding the cure rate can be drawn only after 1700 days or approximately 5 years of observation. After 1700 days, when no more than 7 patients (2.4 %) had not yet reached a 5-year observation period, 83 patients (29.2 %) were presumably symptom-free, while 18 (6.3 %) were lost, and 116 (40.8 %) had relapsed. The longer observation periods do not allow of definite conclusions regarding the total series; but the courses

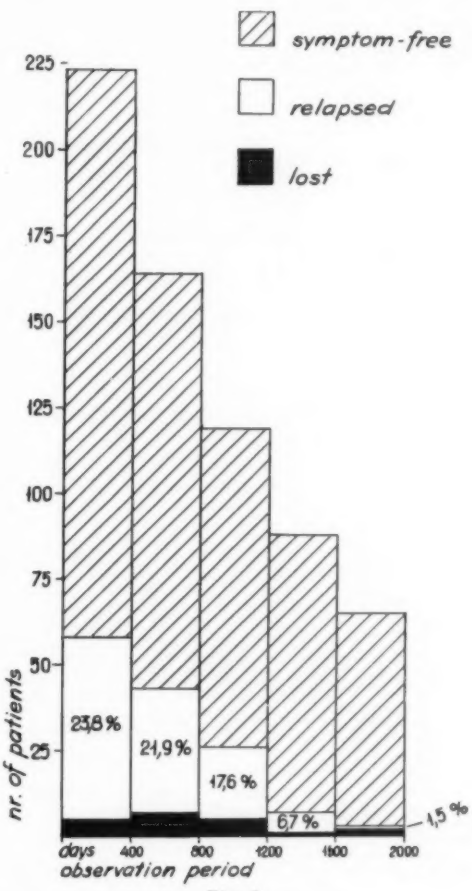

Fig. 2.

The number of observed patients within intervals of 400 days of observation.

of the curves seem to suggest that the percentage numbers of symptom-free will fall after a longer period to somewhat below 30 and that of relapses rise to somewhat above 40.

Fig. 2 shows the patients controlled within periods of 400 days of the observation period. The incidence of relapse is seen to have fallen from 23.8 % within the period of 0—400 days to 1.5 % within that of 1600—2000 days.

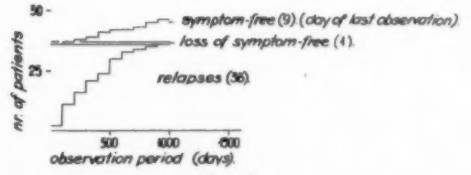

Fig. 3.

Observation of 46 patients who became symptom-free after the second treatment. It is seen how the series of patients was reduced by loss and relapse. Further, the diagram shows the day of the last examination of the still symptom-free patients.

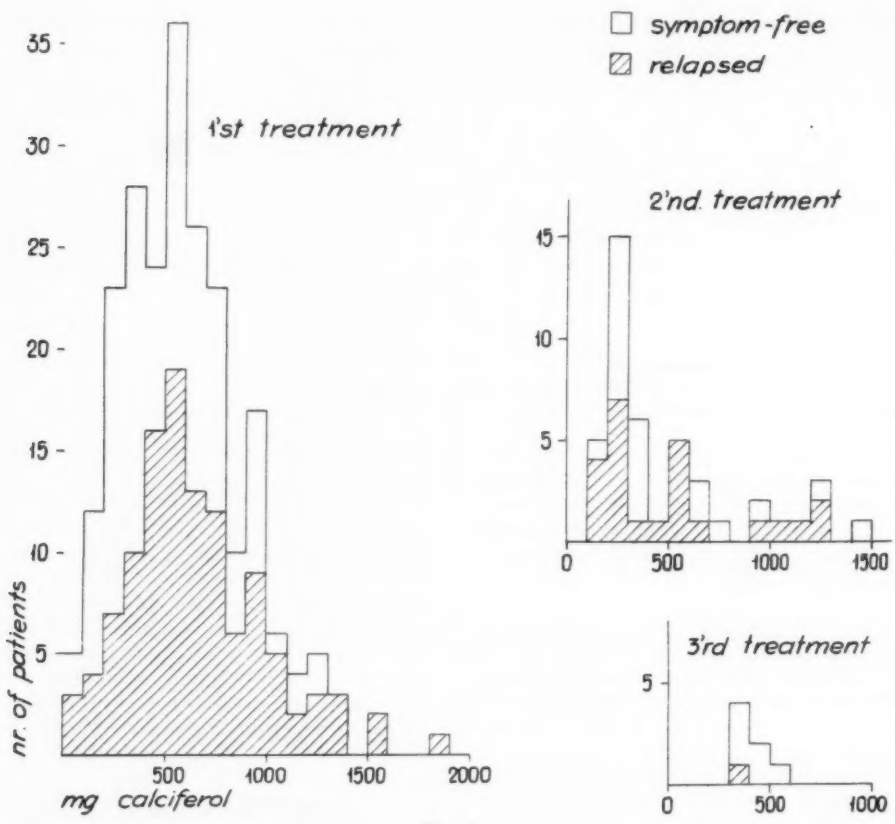

Fig. 4.
Maximum calciferol dose employed to obtain clinical freedom from symptoms. The diagram shows the number of relapses and patients symptom-free after one to three treatments.

Fig. 3 gives a survey of the 46 patients who became symptom-free after the second treatment. The percentage values were here, too, calculated on the basis of the original number of patients (101).

It is seen that one patient (0,9 %) had been lost by death, while 36 (35.6 %) had relapsed, and only 9 (8.9 %) were symptom-free. The relapses had also in these cases occurred after 100—1000 days of observation. Only a 400 days observation period allows of definite conclusions regarding the total series. By this time only two patients (1.9 %) had been observed for less than one year. 22 (21.8 %) were symptom-free, and 21 (20.8 %) had relapsed after one year.

After 2 years, when six patients (5.9 %) had not yet reached a 2-year observation period, 11 patients (10.9 %) were presumably symptom-free, whereas 34 (33.7 %) had relapsed. The incidence of relapse was much higher after the second treatment than after the first, and there is reason to suppose that only very few patients will be symptom-free after a fairly long observation period.

Following the third treatment, five of seven symptom-free relapsed after a short observation period.

DOSE OF CALCIFEROL

As the dose, in conformity with Sonne's principle, varied according to the patient's tolerance, it has been impossible to give a survey of the daily doses employed.

Fig. 4 illustrates the doses with which freedom from symptoms was obtained during the first three treatments. This dose is seen to have had no influence on the ratio between lasting freedom from symptoms and relapse. Fig. 5 shows the total doses given for the first three treatments. The total dose likewise seems to have had no influence on the ratio between freedom from symptoms and relapse; but a relatively great number of patients did not become symptom-free after a small total dose in the first and second treatments.

Table 3 shows the approximate average doses given in the various groups. It is seen that the relapsed cases generally had been given the

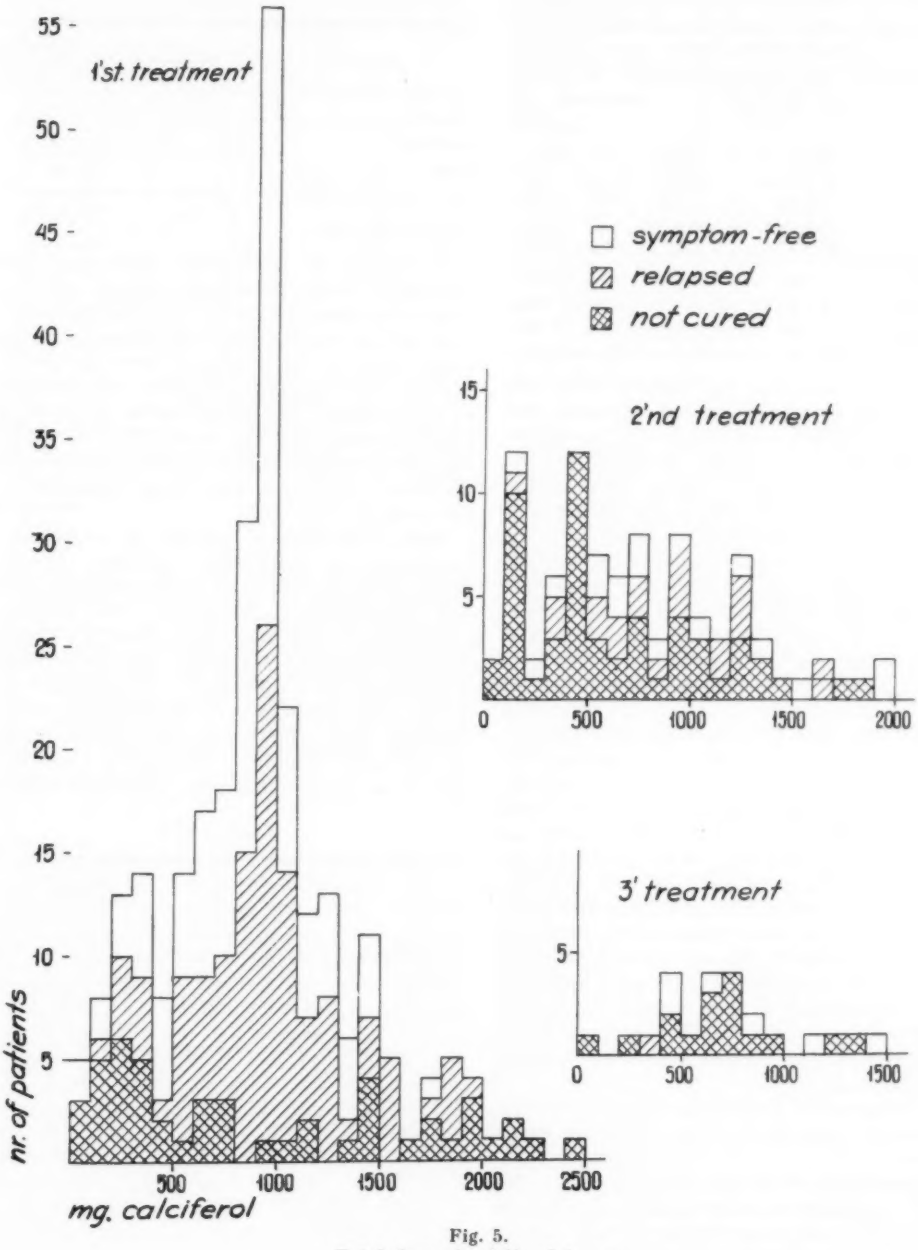

Fig. 5.
Total dose of calciferol in mg.

largest doses, and that the average doses were smaller in the second and third treatments than in the first. The non-cured had received fairly large average total doses, especially in the third treatment, where we made a point of attaining to a result.

INTOLERANCE

According to S o n n e's principle of dosage, the concept of intolerance must be based on a clinical estimate of the patient's chances of tolerating an effective dose. Out of 410 series of treatment 113 did not lead to freedom from symptoms, and on a clinical estimate 85 of these patients were intolerant of an effective dose. In Table 4 the percentage values for the signs of intolerance in the total series of cases are compared with the corresponding values among these 85 patients. For comparison, the signs of intolerance are set out for the 36 patients with spread of tuberculous

Table 3.
Survey of approximate average doses of calciferol (mg).

	Dose till freedom from sympts.		Total dose		
	symptom-free at concl. of exam.	relapse	symptom-free at concl. of exam.	relapse	not cured
1st. treatment	550	600	900	950	(700)
2nd. treatment	350	500	750	800	(600)
3rd. treatment	400	(400)	600	(400)	700

processes. It is seen that intolerance often was assessed on the basis of low urea clearance, elevated blood pressure, and fever. In the group with tuberculous complication, fever and an elevated E. S. R. were more frequent than in the remaining series, and elevated blood calcium and blood urea likewise somewhat frequent.

That S o n n e's procedure of treatment was appropriate appears from the fact that we rarely obtained freedom from symptoms by giving another course of treatment, if the patient had not become symptom-free during the preceding one. Out of 20 patients who carried through the second treatment after not having become symptom-free during the first, only three became symptom-free. Out of five patients who were not symptom-free after the first and second treatment, none obtained freedom from symptoms after the third and fourth treatments. Out of 81 patients who had been symptom-free after the first treatment, but had relapsed, 43 became symptom-free after the second treatment, and six out of 11 after the third. Of the patients who were symptom-free after the first and the second treatment, but not after the third, only one became symptom-free after the fourth treatment, and of seven patients who were symptom-free after the first treatment, but not after the second, two became symptom-free after the third treatment.

Thus, it seems as if patients intolerant of an effective dose are separated out during the treatment.

Simple comparison of the patients given more than one treatment shows a marked aggravation of the signs of intolerance (Table 5).

The tolerance is thus seen to be definitely reduced during treatment with calciferol in the large doses given here.

Table 5.

Tolerance	Comparison of 2nd. and 1st. treatment	Comparison of 3rd. and 2nd. treatment
Worse	59	17
Unchanged	33	5
Better	9	1

Contraindication.

In contrast to the relative tolerance, contraindication shows itself very clearly. In sixteen series of treatment (3.9 %) the treatment must be regarded as having been absolutely contraindicated. *Four* of these patients had febrile intoxication, *three* cerebral symptoms in consequence of hypertension, *six* exacerbation of an existing heart disease, and *three* exacerbation of an existing renal disease. In nine (2.2 %) of these cases treatment would not have been instituted with our present experience.

Contraindication on account of spread or exacerbation of tuberculous infection has been discussed elsewhere (10). According to our present experience, the treatment was contraindicated in at least *ten* cases: *four* of erythema induratum, *four* of cavernous and *two* of infiltrative pulmonary tuberculosis. By adequate combination with antibiotics it is doubtful, however, whether organ tuberculosis is a contraindication of calciferol treatment, whereas it must be regarded as proved that pure calciferol treatment

Table 6.

Cause of death	During treatment	During observation		Total
		Among cured	Among non-cured	
Cancer	1	5	2	8
Heart - lungs	4	2	1	7
Cerebral haemorrhage	1	6	2	9
Uraemia	1			1
Cachexia	1			1
Pulmonary tuberculosis	2	1		3
Renal tuberculosis	1		1	2
Old age		2		2
	10	16	6	33

Table 4.

Signs of Intolerance	Series of treatment	Elevated blood urea	Low urea clearance	Elevated blood calcium	Elevated blood pressure	Subj. troubles	Elevated E. S. R.	Fever
In all series	410	31.3	20.8	75.7	29.2	58.1	58.7	1.8
In pts. regarded as intolerant (excl. tub. compl.)	85	30.6	30.6	72.9	43.5	64.7	61.3	4.7
In pts. with tub. complicat.	36	36.7	18.4	81.6	28.6	65.3	83.7	6.1

Table 7.

Age	Cause of death		Total
	non-tub.	tub.	
30—40	1		1
40—50	1	2	3
50—60	5		5
60—70	12	1	13
70—80	7	2	9
80—90	2		2
	28	5	33

with the dose indicated is definitely contraindicated in cases of erythema induratum and pulmonary tuberculosis. As regards renal tuberculosis, the examinations carried out before the treatments are too deficient to allow of definite conclusions.

CAUSES OF DEATH

Tables 6 and 7 show the causes of death of the 33 patients who died during the periods of treatment and observation. The relative numbers correspond fairly well to the relative lengths of these periods, and the age distribution presents nothing extraordinary. A further analysis of the causes of death was impossible, but there is no evidence to suggest that the treatment had any influence on these.

DISCUSSION

By the method employed, consisting in treatment with 4.5 mg calciferol daily, and after 3 weeks individualisation of the dose, freedom from symptoms was obtained in 78.5 % of the treated patients. 16.5 % did not become symptom-free, chiefly owing to intolerance of the effective dose. A total dose of 500—600 mg calciferol is generally required, but in some cases 1 g or more is necessary, and in some 2 g. Very little is obtained by re-treating non-cured patients, and re-treatment of relapsed cases also has less and less effect, an increasing number of patients becoming intolerant. The treatment can be carried through without appreciable complications, if carefully regulated, especially with a view to blood calcium, blood pressure, and renal function. In no more than 3.9 % of the cases did the treatment give rise to contraindicating complications. Of these, 2.2 % (exacerbation of existing cardiac and renal diseases) could have been avoided, while 1.7 % were impossible to foresee (febrile intoxication, hypertensive syndrome). Tuberculous complications were observed in 12.7 %, but the majority were not dangerous. At least 3.5 %, among which most of the severe complications could have been avoided if erythema induratum and active tuberculosis in other organs had been recognized as contraindications.

The treatment seems in no case to have had an unquestionable influence on the cause of death. The risk must therefore be regarded as relatively small, if contraindications are considered and the treatment is carried through under careful control.

The late results were rather disappointing. Only 29.2 % of the original series had not relapsed after an average observation period of 5 years. The percentage of cure of the primarily symptom-free patients was 37.2 % and thus more unfavourable than the results reported by Pogorzelski and Miedzinski (14). According to the course of the relapse curve, relapses seem to cease or become rare after 1500 to 2000 days of observation.

SUMMARY

284 patients suffering from lupus vulgaris were treated with calciferol alone and kept under regular control from 1946-8 to 1955. The series of cases was selected with a view to the possibility of observation, and of the relapse-free cases only 20 (7 %) were lost by death (15), emigration (4), and interfering surgical treatment (1).

If account is taken of contraindications (diseases of the heart, lungs, and kidneys, erythema induratum, and active organ tuberculosis), the stated methods of treatment and control make it possible to reduce contraindicating intoxications to 1.7 % (febrile intoxication, hypertension) and spread of benign tuberculous processes to less than 9.2 %.

The patients who were not cured, chiefly owing to intolerance of an effective dose, constituted 16.5 % after the first treatment. The succeeding treatments of relapsed cases resulted in a rise in the percentage of non-cured and in the tendency to signs of intolerance. It was rarely possible to cure patients who did not become symptom-free after the first treatment.

78.5 % were symptom-free after the first treatment, but the cure rate fell to 45.6 % and 30.4 % after the next two treatments. Relapse occurred particularly after 100 and before 1000 days of observation, thereafter to be rare. The total number of symptom-free after 5 years of observation from the conclusion of one treatment was 29.2 % of the originally treated patients and 37.2 % of those who became symptom-free. The percentage values decreased considerably after the second and the third treatment. One year after the end of the second treatment only 21.8 % had not relapsed, and 2 years after no more than 10.9 %. There is reason to suppose that the number of symptom-free after several years of observation will be just under 30 % after one successful treatment, whereas the number of symptom-free after two or more treatments will fall to considerably below 10 %.

An average dose of 500 to 1000 mg calciferol is required to obtain freedom from symptoms,

and a total dose of 1000 to 2000 mg is advisable. Calciferol should theoretically be suitable for combined treatment with INH and PAS, owing to its effect on the tuberculous tissue. This combined treatment has been used for some time with excellent primary results and will be compared to the results of treatment with INH and PAS alone. An observation period of 5 years seems, however, to be a necessity.

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ON THE RECOGNITION OF DISTURBANCES IN THE ACID-BASE METABOLISM

By POUL ASTRUP

The definition of acidosis as a condition with decreased CO_2-content ("bicarbonate") in the plasma is widespread, but may be misleading as pointed out by several authors, e. g. Van Slyke (1932). The widespread use of the methods for determination of the CO_2-content of plasma and the predominant interest in metabolic disturbances have been conducive to this situation.

In purely metabolic disturbances in the acid-base metabolism, the pH changes in the blood will follow changes in the CO_2 content. In cases of mixed metabolic and respiratory disturbances this need decidedly not be the case, and in purely respiratory disturbances the pH will vary inversely with the CO_2 content. Therefore, in practice, conditions will frequently be encountered where an isolated determination of the CO_2 content of the plasma will be insufficient to permit an evaluation concerning the cause of a possible change. An extreme lack of correlation between the pH of blood and the CO_2 content of plasma has been confirmed in investigations of about 350 patients with respectively metabolic, respiratory and mixed metabolic-respiratory disturbances. These results have been published elsewhere (Astrup, Götzsche and Neukirch, 1953; Astrup, 1954). It was therefore clearly desirable to introduce more relevant measurements than the determination of CO_2 in plasma, and especially to be able to distinguish between the influence of respiratory and metabolic factors in every single case.

In the following, a theoretical review of these problems will be attempted. It has been the aim to establish definitions and terms relevant for the characterization of disturbances in the acid and base metabolism, and to decide which analytical results will be necessary to secure the correct diagnosis.

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Aided by grants from the King Christian X's Foundation.

DEFINITIONS AND THEORY

In order to understand fully the problems inherent in the neutrality regulation of the organism, it is important to be completely aware of the theoretical background, and to employ definitions and terms which are unequivocal and clear and which are related both to the practical measurements necessary to establish the diagnosis, to the condition of the patient and to the therapy which will be indicated.

In order to further the clarity it should be convenient, as suggested by several authors (Devor, 1953; Prætorius, 1954 and Relman, 1954), to base changes in the designations which are now ordinarily employed in medical terminology on the widely accepted definitions of acids and bases introduced by Brønsted. Prætorius (1954) has thoroughly considered this problem and has shown that considerable increase in clarity is achieved by using these def-

initions, especially while this permits the consideration of acid-base metabolism independently of the cation metabolism. According to Brønsted's definition, acids are characterized through the ability to give off hydrogen ions, while bases are characterized through the ability to accept hydrogen ions. Thus H_2SO_4 is an acid because it may give off hydrogen ions, while SO_4^{--} is a base because it is able to accept hydrogen ions. The bicarbonate ion, HCO_3^- is both acid and base, as it may accept as well as give off hydrogen ions. Within the physiological pH range, however, it will always act as a base.

According to this definition the cations in the plasma (Na^+, K^+, Ca^{++}, Mg^{++}) are neither acids nor bases and should accordingly not be designated bases (e. g. "total bases"), but cations.

Instead of the expression acid-base balance it would be more appropriate, as suggested by Warburg (1954), to talk of the acid-base *metabolism* of the organism. The expression acid-base *status* is appropriate to characterize the immediate state of the organism as revealed through a single examination. Some other frequently employed expressions should also be changed, but as the justification for these changes will be most evident from an accompanying consideration of the circumstances, which should be taken into account in measurements for determining the acid-base status, they will be treated as they arise in the following.

Every accumulation in the organism of acids (carbonic acid or other acids) will involve an increase in the hydrogen ion concentration in the plasma. An accumulation of base will have the opposite effect.

A measurement of the pH in the blood (plasma) will accordingly be relevant in order to establish the presence of a surplus of either acid or base independently of the kind of acid or base.

Moreover, it will be desirable to establish whether a change in the pH is due to disturbances in the elimination of carbonic acid through the lungs, or to non-respiratory changes in the acid-base metabolism. This may be achieved by measuring the total carbon dioxide in plasma in addition to the pH.

The total-CO_2 in plasma will be determined by two quantities, firstly the amount of base (OH^-) available for the binding of CO_2 as bicarbonate, and secondly the carbon dioxide tension in the gas mixture, which will be in diffusion equilibrium with the plasma. The larger the available amount of base, the larger will be the total-CO_2, when the pCO_2 is unchanged. Similarly at a constant available amount of base, the total-CO_2 will be larger the larger the pCO_2.

In order, therefore, to obtain a quantitative measure of the extent of the disturbance, it is necessary instead of the total-CO_2 to determine the amount of base available for binding CO_2 and also the pCO_2. The concentration of available base for binding CO_2 is expressed through the magnitude of the bicarbonate content in plasma separated from blood at a fixed pCO_2. Usually a pCO_2 of 40 mm Hg is employed, as first suggested by Hasselbalch (1917). This quantity measures changes in acid-base metabolism, which are described as metabolic (i. e. non-respiratory). Respiratory changes, on the other hand, will be expressed through the magnitude of the pCO_2 in the blood. This again is dependent on the magnitude of pCO_2 in the alveolar air and thus of the alveolar ventilation. The three quantities which will accordingly be relevant, and which it will be of decisive importance to know, when an accurate acid-base status is desired, are: *pH, pCO_2 and the bicarbonate concentration in plasma separated from blood at a pCO_2 of 40 mm Hg.* This last named quantity may be called the standardised bicarbonate or *standard bicarbonate.* Its variation with the concentration and the oxygenation of hemaglobin is described in a subsequent paper (Astrup, 1955).

The word "bicarbonate" is usually employed in medical terminology to designate the total content of CO_2 in a plasma sample. As will be evident from the preceding treatment, this is only correct as far as the actual bicarbonate concentration is concerned — and even then only partly so — as this will always be about 90—98 per cent of the total-CO_2.

Instead of "bicarbonate" to signify the total content of CO_2, the expression total-CO_2 should be employed, and the word bicarbonate should only be applied when it is qualified as either the actual bicarbonate concentration or as the standardised bicarbonate concentration. The most common expression to cover what has been defined here as the standard bicarbonate has hitherto been "alkaline reserve". This expression should, however, be avoided if only to be in agreement with Brønsted's definitions. By employing the expressions suggested here, the content of the individual conceptions will hardly be subject to doubt. Reference is made to Table 1.

So far the words *acidosis* and *alkalosis* have been used by many to signify a condition with a decrease or an increase, respectively, in the total-CO_2, not caused by respiratory disorder. These expressions should, however, refer to all conditions with an accumulation or decumulation of acid or base so that the expressions *respiratory acidosis* and *respiratory alkalosis* refer to conditions with a primary increase or decrease of pCO_2 from respiratory causes, while the expressions *metabolic acidosis* and *metabolic alkalosis* should be used to characterize conditions with a primary decrease or increase, respectively, in standard bicarbonate from other than respiratory causes.

Furthermore, to each of these 4 expressions the terms *uncompensated, partially compensated* or *fully compensated* may be attached. The or-

Table 1.
Definitions, designations and symbols.

Designation:	Symbol:	Definition:
Carbon dioxide tension	pCO_2	The partial pressure of dry carbon dioxide in diffusion equilibrium with blood. Expressed in mm Hg.
Total carbon dioxide or total-CO_2	total-CO_2	Total concentration of carbon dioxide in blood or plasma, which is measurable after expulsion through addition of acid. Expressed in mMol/L.
Actual bicarbonate concentration	actual HCO_3^-	Bicarbonate concentration in plasma at the pCO_2 actually present. Expressed in mMol/L.
Standardised bicarbonate concentration or standard bicarbonate	Standard HCO_3^-	Bicarbonate concentration in plasma separated from blood after equilibration with carbon dioxide at a fixed pCO_2 of 40 mm Hg. Expressed in mMol/L.
Physically dissolved carbon dioxide	CO_2	Amount of carbon dioxide dissolved in the liquid without being converted to bicarbonate or carbonic acid. Expressed in mMol/L. (together with the carbon dioxide content).
Carbonic acid	H_2CO_3	Concentration of carbonic acid. The amount is vanishingly small, (few micro moles per liter).

ganism itself attempts to correct disturbances in the acid-base metabolism in such a way that the normal pH is approached. Primary changes in the standard bicarbonate may thus be compensated with regard to pH by changes in the same direction in pCO_2, while primary changes in pCO_2 may be compensated by changes in the same direction in standard bicarbonate.

The expression *partly compensated metabolic acidosis*, for instance, involves that there is a reduction in standard bicarbonate, and that the organism compensates the decrease in pH by increasing the ventilation and thus reducing the pCO_2, and that this reduction is not sufficient to change the pH to the normal value.

APPLICATIONS OF THE DEFINITIONS

In Table 2 examples of the 4 main types of disturbances are shown: the respiratory acidosis and alkalosis, and the metabolic acidosis and alkalosis. In the explanation to the table the relation between the clinical condition and the results of the laboratory analyses are to be found.

Table 2.
pH, total-CO_2, pCO_2 and changes in standard bicarbonate in patients with respiratory acidosis and alkalosis (No. 1 and 2) and metabolic acidosis and alkalosis (No. 3 and 4).

Patient No.	a/v blood	pH	Total-CO_2 mMol/L.	pCO_2 mm Hg	Change in standard bicarbonate mMol/L.
1.	v	6,99	39,0	150	÷ 1,6
2.	a	7,65	15,6	14	0
3.	a	7,03	4,9	16	÷ 16,4
4.	a	7,55	46,0	55	+ 18,8

Explanation to Table 2:

Patient No. 1. The figures relate to a patient with respiratory paralysis immediately after admission to the hospital. The patient was subventilated to an extreme degree, nearly moribund. A strongly reduced pH, increased total-CO_2 in plasma and a considerably increased pCO_2 of 150 mm Hg were found. The standard bicarbonate, on the other hand, was not with certainty pathological, so no metabolic disturbances were present. The final laboratory diagnosis should therefore be: uncompensated respiratory acidosis.

Patient No. 2. The same patient as above, 3¼ hours later after tracheotomy had been performed and artificial respiration given through some time. The pH is now increased, the total-CO_2 in plasma decreased and the pCO_2 reduced to 14 mm Hg.

The standard bicarbonate is still within normal limits. The final laboratory diagnosis is: uncompensated respiratory alkalosis.

Patient No. 3. A patient with diabetic coma. The pH, total CO_2 and pCO_2 in plasma are reduced. The change in standard bicarbonate is ÷ 16.4 mMol. The laboratory diagnosis is: partially compensated metabolic acidosis.

Patient No. 4. The patient had a pyloric stenosis with a chloride concentration in plasma of 50—60 mEq/L. Increased pH, a strongly increased total-CO_2 and a moderately increased pCO_2 is found. The change in standard bicarbonate is + 18.8 mMol. The laboratory diagnosis is: partially compensated metabolic alkalosis.

In Table 3 some analytical results are shown from a man, 44 years old, suffering from chronic epidemic encephalitis. He was admitted to the medical department of the Blegdamshospital on the 18th Dec. 1953 after having suffered from sudden respiratory difficulties a few days before. The respiration after admission was very super-

ficial and intermittent. He was, however, able to breathe regularly when told to do so. Nothing abnormal was found in the lungs. In the course of some days anuria developed, probably caused by anoxaemia. He was treated with oxygen; artificial respiration was attempted. He died on the 24th Dec. at 8^{45} a. m.

Table 3.
pH, total-CO_2, pCO_2 and change in standard bicarbonate in arterial plasma from a patient with respiratory acidosis and (commencing) metabolic acidosis.

Date	pH	Total-CO_2 mMol/L.	pCO_2 mm Hg	Changes in standard bicarbonate. mMol/L.	Oxygen saturation per cent
Dec. 19	7,36	28,3	50	+ 0,3	70
— 20	7,32	28,3	56	+ 2,2	96
— 21	7,22	30,0	74	÷ 0,1	91
— 22	7,37	23,0	39	÷ 1,2	86
— 23	7,27	23,2	50	÷ 4,1	71

The analyses performed show that on the 19th and 21st of Dec. the disturbance in the acid metabolism is purely respiratory: pCO_2 is increased and the diagnosis will be: uncompensated respiratory acidosis. In spite of oxygen treatment the oxygen saturation of the blood is lowered.

It was to be expected that indications of metabolic acidosis would appear during Dec. 22nd and 23rd due to the kidney disease as the concentration of non-protein nitrogen increased during this period from a normal value to 147 mg pr. 100 ml. The figures show, in fact, that the change in standard bicarbonate from the earlier positive value now becomes negative and on the 23rd it is definitely pathological. The laboratory diagnosis for this day accordingly becomes: metabolic acidosis plus respiratory acidosis.

It should be pointed out that the total-CO_2 in all examinations was within normal limits. The separation of the metabolic and respiratory components shows distinctly how the gradual development of the acidosis of renal origin may be observed.

DISCUSSION

As suggested by several authors Brønsted's definition of acids and bases should be employed in medical terminology. This will involve a change in the meaning of certain expressions now commonly used. Furthermore, the present usage is in several respects likely to cause misunderstandings, especially with regard to the expression acidosis, and the designation of the measurements on which the diagnosis of the disturbance is based, in particular the use of "bicarbonate" instead of total-CO_2.

In accordance with Prætorius (1954) a change is therefore suggested in the terminology now employed. There can hardly be any doubt that general acceptance of the new terminology will help to avoid misunderstandings, not only between physicians and non-physicians, but also in the realization of the nature of disturbances in the acid-base metabolism.

In Anglo-Saxon literature the terms "acidaemia" and "alkalaemia" are often used to characterize conditions with reduced or increased pH in the blood, respectively, while acidosis and alkalosis refer to conditions with reduced or increased content of CO_2 in the plasma. It appears more relevant, as suggested in the present work, to separate directly through measurements the respiratory and metabolic components in the individual cases, and to express them through pCO_2 and the bicarbonate concentration in plasma, separated from blood at a pCO_2 of 40 mm Hg, respectively. By means of these two quantities and the pH of the blood, the condition may be characterized in a satisfactory manner. In order that the definitions and terms suggested may be of value also in the everyday clinical work, it is necessary, however, that relatively simple and reliable methods should be available to determine these three quantities (*pH, pCO_2* and *standard bicarbonate*). Such methods based on electrometric measurements and normal values are published elsewhere (Astrup, 1955), where the theoretical background for these methods is also discussed thoroughly in the light of the classical investigations in this field.

It is not sufficient, in order to characterize a disturbance in the acid-base metabolism, to perform only one of these measurents, either of the content of total-CO_2 in the plasma, the bicarbonate content at a pCO_2 of 40 mm Hg (= the "alkaline reserve") or the pH of the blood. Only through integration of all three values in the way described is it possible to obtain a correct picture of the condition and accordingly valuable guidance with regard to the therapy which should be instituted. The practical importance of this is discussed elsewhere (Astrup, 1954).

If one is only interested in establishing the degree of metabolic disturbances — as is most often the case in the clinic — a measurement of the standard bicarbonate alone should be performed. This measurement is extremely simple, especially in serial analyses, and the results are very uniform in normal subjects, in 80 per cent of the cases within ± 1 mMol/L. (Astrup, 1955), while the variations in the total-CO_2 is stated by most authors to be about ± 4—5 mMol/L.

Finally, it should be pointed out that the distinction between respiratory and metabolic components made in this paper has been applied previously in physiology and experimental medicine, in fact first by Hasselbalch (1917), who introduced the "reduced" and the "regulated" pH in blood.

SUMMARY

The definitions and terminology which are considered adequate to describe disturbances in the

neutrality regulation of the organism are discussed in considerable detail. The theoretical relations are mentioned, and it is shown that the quantities which are relevant, and which it will be necessary to know in order to diagnosticate disturbances in the neutrality regulation are: the pH of the blood, the carbon dioxide tension, and the concentration of bicarbonate in the plasma at a carbon dioxide tension of 40 mm Hg.

Examples are given of practical application of the definitions suggested.

Acknowledgement.

The values in Tables 2 and 3 concern patients admitted to the Blegdamshospital. For permission to publish this material I am indebted to Prof. H. C. A. Lassen and Chief Physician M. Bjørneboe.

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SUAVITIL IN THE TREATMENT OF PSYCHONEUROSES

By OLAF ØSTERGAARD JENSEN

Suavitil is the hydrochloride of benzilic acid diethylaminoethylester. It has a peripheral anticholinergic effect and a specific effect on the central nervous system. In normal persons 4—6 mg induce a peculiar blocking of the spontaneous associations, by one observer described as a maximal absent-mindedness, but the central effect is particularly pronounced when the subjects are exposed to psychic stress. In animal experiments with cats (Jacobsen and Skaarup, 1955) and with rats (Jacobsen and Sonne, 1955) certain stress-induced behaviour patterns are normalized by Suavitil. In human experiments Suavitil abolished or diminished the vegetative responses to emotion (e. g. skin temperature in the face, pulse frequency, etc.) (Jacobsen et. al., 1955). Therefore, it was found worth while to submit this compound to a clinical trial. Some clinical, preliminary experiments have been made by Munkvad (1955). Here a more detailed analysis of the clinical effect on psychoneuroses in presented.

The experiment is carried out in the *Danish Red Cross Sanatorium, Hald.* Some 2000 patients from the whole country are yearly submitted to treatment here, by general practitioners or other hospitals. About a third of these are psychoneurotics.

Material.

In all 110 patients have been treated: 44 males and 66 females. The average age has been 40 years (16—75) for the males and 39 years (15—76) for the females. Most of the patients had been treated in several other hospitals before they were admitted to the sanatorium. 96 of the patients have been treated in the sanatorium, 14 only ambulatory. Ten of the hospitalized patients have continued their medication ambulatorily after discharge.

The Suavitil group is compared with a control group of 110 patients treated during the same period, picked out at random, but so that approximately the same types of patients are represented in both groups.

All patients have been submitted to our usual routine therapy consisting of occupational therapy, physical therapy, and psychotherapy in the form of personal interviews. The patients in the experimental group received no other sedatives than Suavitil (or placebo), while the patients in the control group were given barbiturates (pentothal or phenobarbital, the latter often combined with bromides), corresponding to the routine medication used here for psychoneuroses during the past years.

The patients have generally been treated during their total stay in the sanatorium — an average of 70 days. The ambulatory patients were treated during a similar period.

ASSESSMENT OF THE RESULTS

The following terms have been used in the assessment of the results:

"Good effect": Practically all neurotic symptoms have disappeared, and the remaining symptoms are only slightly disturbing. The effect exceeds the average.

"Moderate effect": Important neurotic disturbances have been abolished. Some symptoms remain, but the patients state spontaneously a considerable improvement.

From The Danish Red Cross Sanatorium, Hald, Viborg, Denmark.

"No effect": Means that the effect is uncertain. Some patients are not necessarily unimproved, but here the result is merely what could be expected according to our experience with patients of this type.

The assessment is based on the patients' own statements and our impression of the patients' willingness to accept a psychotherapeutical explanation and cooperate in the therapy. Moreover, their general behaviour in the wards was observed by the nurses, especially their relations to the daily routine and their fellow patients. The "normal progress" is well known by our experienced personnel. In no cases did the assessments of the different instances disagree.

Table 1.
All-over results in the experimental group and in the control group.

Effect	good	moderate	one	total number of pts.
Controls ..	25 (23%)	28 (25%)	57 (52%)	110
Patients treated with Suavitil ..	56 (51%)*)	19 (17%)	35 (32%)	110

*) P 0—1 %

RESULTS

Table 1 shows the all-over results obtained after three weeks' treatment with varying doses. There is no difference between the reactions of male and female patients. In some cases the effect of Suavitil medication was very striking as shown in the following example of case histories, which also gives an idea of the type of patients treated:

Case A: Married female patient, 28 years old.
Psychoneurosis with depressive reaction.

She had previously been completely healthy. She married eight years ago, but three years ago her husband suddenly disappeared and joined the Foreign Legion and was sent to the war theatre in Indo-China. He never sent her money, and she had to work in order to support herself and her two children. Her work was some distance from her home, and the whole situation gave her many worries. She was anxious about her husband, whom she still loved in spite of the fact that she despised his lack of responsibility. She reproached herself that she neglected her children. Her many speculations overcame her after all. She felt exhausted and sick and slept badly. Upon admittance to the sanatorium she had completely lost her spirits, was out of balance, irritable, and wept frequently. Somatically, she complained of muscular pain and showed objectively strong muscular tension.

During the first ten days of her stay she was given pentobarbital without improvement. During the following eight days 0.5 mg Suavitil t. i. d. was without effect. The dose was subsequently increased to 1 mg t. i. d. Her spirits almost immediately improved, she felt much more able to judge her situation, and her sleep improved. After three weeks' medication the Suavitil tablets were substituted by placebo tablets. Three days after all her former symptoms reappeared, and her thoughts became again chaotic. After ten days she again was given true Suavitil tablets with the effect that she again felt improved, resolved to divorce her husband and move to another town, where she could be able to do more for her children.

Case B: 56-year-old male, married.
Psychoneurosis with anxiety reaction and obsessive-compulsive traits.

For many years he had worked as a technical supervisor in a big industrial firm, frequently under hard pressure. From time to time he found the personnel difficult to manage. He always wanted perfect work, and when occasionally something went wrong he felt extremely worried. Moreover, as extremely polite conduct always has been an unwritten law in his working place he has had no possibilities of ab-reacting his worries. During the last years he began to doubt his abilities, and he felt anxious and uncertain towards the personnel and with himself. He feared to commit suicide. The state developed into considerable depression, he was tired, and ruminated constantly. Prior to his admittance to the sanatorium he was treated with pentobarbital and phenobarbital without effect.

After his admittance he was at once given Suavitil, 1 mg t. i. d. Aften a few days his behaviour became more natural, and later he subjectively stated that his anxiety was reduced. After twelve days Suavitil was substituted by placebo tablets. His anxiety and compulsive thoughts soon returned, and he was further depressed, because he found his initial progress stopped. Twelve days later he again was given Suavitil, and the symptoms rapidly disappeared. He regained his self-confidence and energy, and felt that he after all was able to manage his job.

Further analysis of the material.

The longer the disease has lasted the poorer the results seem to be, although the difference hardly is significant (Table 2). Some patients revealed no psychic trauma in their histories, in others an apparent psychic trauma was found.

Table 2.
The effect in relation to the duration of the present neurosis.

Result	1 year or less	1-10 years	more than 10 years
Good	14 (64%)	31 (57%)	11 (33%)
Moderate ..	4 (18%)	5 (10%)	10 (29%)
No	4 (18%)	*18* (33%)	*13* (38%)
Total	22	54	34

Some of the latter patients were up against insoluble problems, for example unhappy marriages, which could not be dissolved because of the children, chronic somatic diseases giving a feeling of invalidity among very active patients, frigidity affecting normal sexual intercourse, etc. From Table 3 it can be seen that the effect is considerably less when persistent insoluble problems are present. No statistical significant differences can be seen between the groups of patients with no psychic trauma and those with

psychic traumata, but without "insoluble" problems.

Table 3.
Prognostic factors.

Results	No apparent psychic trauma	Persistent psychic trauma	Persistent insoluble conflicts
Good	7 (46%)	41 (59%)	8 (29%)
Moderate ..	2 (14%)	12 (16%)	8 (29%)
No	*6* (40%)	*16* (25%)	*12* (42%)
Total	15	69	28*)

*) P = 1—2%.

The psychoneurotic disorders with anxiety, neurotic-depressive, and partly with obsessive-compulsive reactions or asthenic reactions seem to be influenced by Suavitil (Table 4).

Table 4.
The effect in the different types of psychoneurotic disorders.

Effect	good	moderate	no	total
Psychoneuroses with:				
Anxiety reaction	5	1	1	6
Obsessive-compulsive reaction	2	3	2	7
Neurotic-depressive reaction	35	5	10	50
Hysterical reaction without anxiety reaction	0	0	4	4
Somatic symptoms*)	1	3	1	5
Asthenic reaction	11	6	11	28
Hypochondrial reaction	1	1	3	5
Endogenous depression	0	1	3	4
Senile dementia	0	0	1	1

*) Myosis, heart troubles, etc. No. cases of gastric ulcer, asthma, etc. have been included in this group.

All patients were submitted to a psychological examination at their admittance. In about a third of the cases the basic constitution could be determined, and the response of the treatment in the different constitutional factors is seen from Table 5. It is remarkable that psychoneuroses developed in a depressive constitution seem to respond well to the medication in spite of the fact that the endogenous depressions do not react.

Table 5.
Basic factors and their influence on the treatment.

	good	moderate	no	total
Endogenous depressive constitution	4	1	0	5
Character neurosis	3	2	2	7
Psychopathy	4	1	7	12
Low I. Q.	1	0	1	2
Climacterium	*6*	2	*3*	*11*

The figures are small, but the trend is clear. On the other hand, a psychopathic constitution diminishes the chances for a good effect of Suavitil. Among the 12 patients with a psychopathic constitution, 3 had depressive reaction (effect in all cases), 4 asthenic reaction (effect in one case), 3 anxiety reaction (effect in one case), 1 an obsessive-compulsive reaction, and 1 a hysterical reaction.

Placebo reactions.

Placebo tablets have been administered to 40 patients, who responded well or fairly well to the Suavitil medication. The patients, the nurses, and my colleagues were unaware which kind of tablets were given. In one case the beneficial effect of the previous Suavitil medication was maintained, and one patient felt better. The others relapsed, but the improvement was regained when Suavitil was given again.

Effective doses and side-effects.

Only a few of the patients reacted to a daily dose of 0.5 mg t. i. d. With a dose of 1.5 mg t. i. d. almost the same effect was obtained as after 1 mg t. i. d. daily, but the higher dose may cause a slight blocking of the thoughts in a few cases.

Only few and insignificant side-effects have been observed. Some patients have complained of a slight dizziness, a slight blocking of the thoughts and an undefined feeling of "queerness". No systemic side-effects have been observed: no icterus, no depression, no Parkinsonism. Complete blood examinations have been made on 50 patients during the whole medication without showing any sign of blood changes. In no cases has Suavitil caused euphoria. Obviously the patients felt better, but this was only a mere restoring of the natural feeling of well-being, and there has never been any tendency to increase the dose.

Effect in ambulantly treated patients.

Fourteen patients suffering from types of psychoneuroses in which a good result could be expected were treated ambulantly. A good result was found in 11 cases, and a moderate in 2 cases. All had previously been treated in vain for a longer time by general practitioners with the common sedatives (especially barbiturates) (10 with a neurotic-depressive reaction, 3 with an obsessive-compulsive reaction, and 1 with asthenic symptoms). Ten of the patients treated in the sanatorium continued the medication after they had been discharged with a continued good result.

It is still too early to assess the lasting results of the medication, but the few available observations seem encouraging. One patient started to work after her discharge in a place where difficulties very frequently arise, but she felt calm and unimpressed even in complicated situations and even after she had discontinued the medication for two months. Five other patients have spontaneously discontinued their medication because they felt completely well.

DISCUSSION

In the cases where an effect was obtained the improvement began after a few days' medication. The patients became more open and sociable, more relaxed, and much better fit for psychotherapeutical measures. A few days later the patients felt a subjective effect. One of the patients described it as follows: His former chaotic thinking decreased and was little by little replaced by plan and system. The rumination preventing the sleep disappeared and the sleep became normal again. He found his fellow patients more kind and conversable. His spirits rose, but without any tendency to euphoria.

In the good cases all symptoms within the psychoneurotic syndrome disappeared, but the trend to speculate and ruminate seemed to be especially early and favourably influenced. The patients felt that a barrier had been established between them and the external influences, especially the purely practical difficulties. This was not caused by lethargy, but by the feeling from the side of the patients that even their problems had a solution. In this way a vicious circle was broken, a better effect of psycho-therapy obtained, and the whole psychoneurotic complex was dissolved with a subsequent improvement.

However, the barrier can be forced if the external noxious influences are too intense. This is confirmed by the observation in Table 3 that patients with insoluble persistent practical problems are less beneficially influenced by Suavitil.

SUMMARY

110 patients with psychoneuroses have been treated with Suavitil (benzilic acid diethylaminoethylester, hydrochloride) — a new drug with a specific effect on the central nervous system. A beneficial effect was obtained in 75 % of the cases, much superior to what could be seen after medication with barbiturates. Especially patients with anxiety reactions, depressive reactions, and obsessive-compulsive reactions responded favourably to the medication.

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ON THE PROTEIN CONTENT OF THE HUMAN FOETUS

A COMPARISON BETWEEN THE CONCENTRATION OF TISSUE PROTEINS IN THE MOTHER AND THE GROWTH IN LENGTH OF THE FOETUS A PRELIMINARY REPORT

By PER PAABY

During a previous investigation on the nitrogen content in human tissues (7), a couple of foetuses were included "at random" in the series of analyses. When a comparison was attempted between the results of the analyses and previous investigations published on this subject, it became apparent that a veritable vacuum existed in the general knowledge concerning the chemical composition of the human foetus.

Von Bezold (11, 12) in 1857 seems to be among the first to deal with the problem which he treated in a series of thorough and animated investigations.

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Aided by a grant from King Christian the Tenth Foundation.

Since von Bezold's time to date, a number of sporadic and rather random investigations have been published, all comprizing rather limited materials of analysis of the foetus in toto, i. e., no attempt being made to determine the composition of the individual organs after dissection. The majority of these results were compiled by Givens (3) who combined them with his own investigations, and the total material was supplemented by Iob (4) in 1934.

On reviewing the literature, my interest was, among other things, drawn to Booker's (1) theory according to which the foetus exists as a parasite upon the organism of the mother while even considerable variations in the "nutritional history" of the mother are not manifest in the chemical composition of the foetus.

A monograph by Shohl (9) originating from 1939 accounts for the chemical composition of

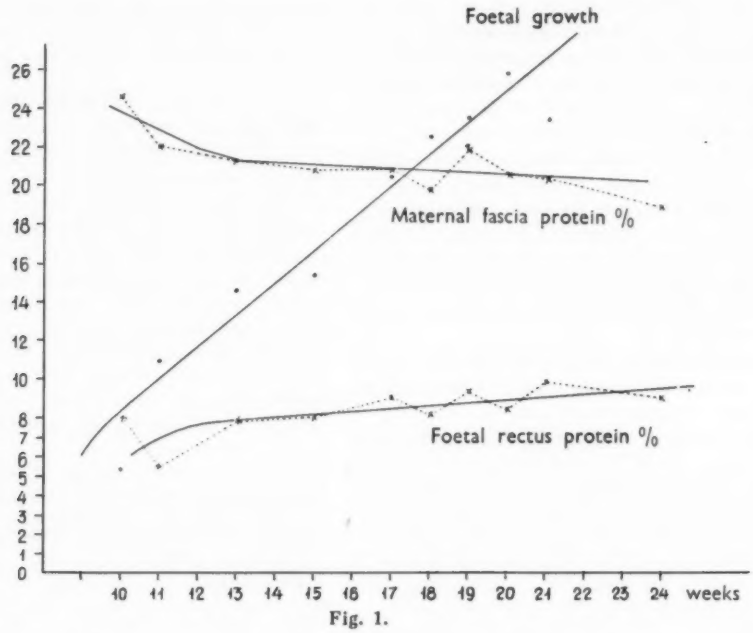

Fig. 1.

foetus in toto. The tables were reproduced by Sundermann (10) in 1950. In 1953, Patten (8) published a table of the growth of the individual organs during foetal life. In this publication, he mentions that the individual organs during "the protected intra-uterine life" grow steadily and equally rapidly while post partum they grow unequally (thymus, genitalia, central nervous system). The chemical composition of the individual organs is not accounted for.

During recent years, Widdowson (13, 14, 15), in particular, has contributed to the analytical investigations. In 1950, she dealt with the chemical composition of foetuses in toto at various stages of foetal life. In a number of cases she investigated, in addition, the chemical composition of placenta.

Of the individual organs, the thyroid gland was investigated in view of the iodine content.

Thus, in none of the investigations published to date did I succeed in finding information concerning the chemical composition of the individual organs at various stages of foetal life. The subject, therefore, apparently requires attention. The publication of the following limited material may be regarded as a preliminary communication. The series of investigations is quite small and is intended as a sample providing orientation as to which problems may be anticipated during the subsequent work whether of practical (analytical, etc.) or theoretical nature. As regards the latter, I have, among other things, had in mind whether biochemical problems might be reflected in the "chemical" foetal development, e. g. in the relationship between the maternal and the foetal organisms.

The material employed originates from patients admitted for therapeutic abortion and consists of 20 foetuses aged from 10 to 24 weeks. In no case was the intervention undertaken on account of physical disease in the mother or anticipated physical disease in the foetus.

In calculating the age of the foetus, the "menstrual age" (6) was employed, calculated from the first day of the last normal menstruation. The foetuses were delivered by abdominal hysterotomy and were, in all cases, perfectly healthy and uninjured. The foetuses were measured from vertex to heel in extended position and from each the upper segments of the precursor of the rectus abdominis muscles on both sides were dissected out. The dissection of special fascial layers was impossible. During the operation, biopsy of the external layer of the mother's abdominal fascia inferior to the umbilicus was performed.

The nitrogen content of the tissue samples was determined by Kjeldahl's method of analysis. The technique of the method was described in a previous work (7).

The results obtained in the individual cases are shown in Figure 1 in tabular and diagrammatic form. The mean curve of growth proceeds without any unexpected deviations. The upper dotted curve shows the protein content of the mother's fascia expressed as percentage of the "wet weight", while the individual points indicate the average of the figures in the table week by week. The upper continuous line levels out the curve and appears to indicate that the protein concentration in the abdominal fascia of the mother decreases during pregnancy. The lower dotted line shows the protein content of the rectus ab-

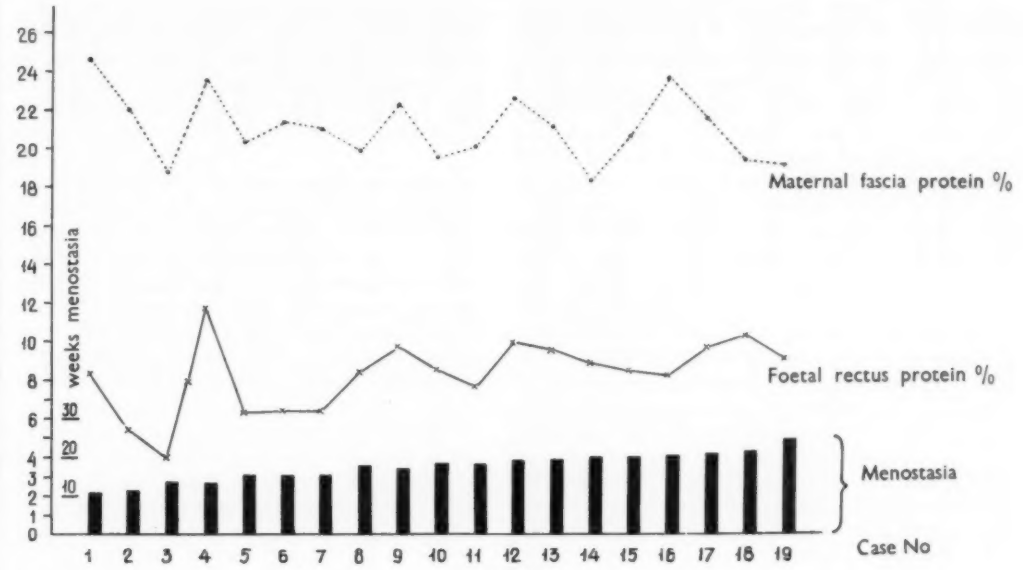

Fig. 2.

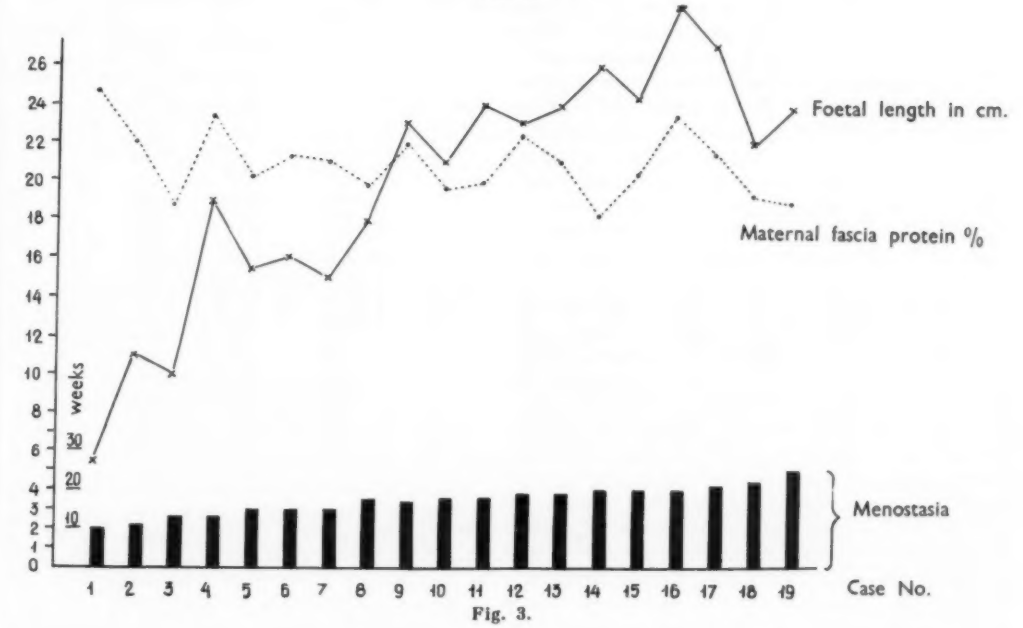

Fig. 3.

dominis sample of the foetuses as percentage of the wet weight and, as previously, each individual point indicates the average from the table week by week.

The leveling out of this curve (lower continuous line) shows that the protein concentration increases with increasing foetal age.

An interesting observation can be made: the two dotted curves appear point by point to vary fairly similarly, *viz.*, higher protein content in the mother renders higher protein content in the foetus.

An attempt may be made to analyze this condition further by plotting the values for the individual cases diagrammatically without computing mean values. Figure 2 shows the values for the individual cases plotted along the abcissa according to increasing menstrual age. A certain correlation seems to exist between the variations of the two curves, particularly in their initial parts.

In Figure 3, in a similar diagrammatic form, the protein content of the maternal fascia and the length of the foetus are compared. Recalling that

Lunar month		III	IV	V	VI	VII	VIII		III	IV	V	VI	VII	VIII
Average	Foetal length in cm	7 cm	14 cm	24 cm	24 cm		42 cm	Foetal weight in grams	25 g	43 g	278 g			1530 g
Min. — max.		5—11	10—19	18—28	22—24				30—20	36—50	220—405			
No of cases		3	8	14	3		1		2	2	8			1

		Organ protein %							Organ protein %					
		III	IV	V	VI	VII	VIII		III	IV	V	VI	VII	VIII
Average	Cerebrum		5.8 %	5.0 %				Ren. dext.		6.2 %	8.5 %			
Min. — max.			5.6—6.0	4.1—6.6						6.2—6.2	7.5—9.3			
No. of cases			2	4						2	6			
Average	Cere-bellum		5.6 %	4.6 %				Ren. sin.		6.7 %	8.7 %			
Min. — max.				4.5—4.7						6.4 - 6.9	8.2—9.4			
No. of cases			1	2						3	6			
Average	Gl. Thyr.		6.5 %	11.1 %				Pulm. dext		5.0 %	7.6 %			
Min. — max.				9.3—12.7						4.0—6.3	6.7 -10.4			
No. of cases			1	4						3	6			
Average	Thymus		5.9 %	10.6 %				Pulm. sin.		5.2 %	7.5 %			
Min. — max.				8.3—11.8						4.2—6.6	6.1—8 3			
No. of cases			1	5						3	6			
Average	Gl. Suprarenal dext.		8.3 %	10.0 %				Ventricel			6.9 %			
Min. — max.			8.0—8.7	8.7—11.6										
No. of cases			3	4							1			
Average	Gl. Suprarenal sin		8.7 %	10.0 %				Lingva		6.7 %				
Min. — max.				8.4—11.0										
No. of cases			1	4						1				
Average	Pancreas			7.5 %				Femur musculi			8.0 %			
Min. — max.				6.7—8.5										
No. of cases				4							1			
Average	Hepar	15.0 %	13.9 %	13.5 %	14.1 %		12.2 %	Diafragma musculum			8.4 %			
Min. — max.			13.3—14.2	11.1—16.5	13.5—14.6									
No. of cases		1	5	13	2		1				1			
Average	Lien		15.6 %	13.9 %			13.8 %	Rectus musculi	6.8 %	7.4 %	8.9 %	9.5 %		12.8 %
Min. — max.				13.0—16.1					5.5—8.2	4.0—11.6	7.6—11.1	9.0—10.1		
No. of cases			1	6			1		2	7	11	3		1
Average	Testes Ovarii		♂ 8.0 %	♂ 8.8 % ♀ 8.4 %				Uterus + salpinges			12.8 %			
No. of cases			1	1 ♂ 1 ♀							1			
Average	Cor		6.2 %	7.4 %			11.4 %	Whole foetus, 6 weeks : 3.4 % protein, 1 case						
Min. — max.			5.5—6.8	6.6—8.2										
No. of cases			3	6			1							

the curve of growth ascends steeply from left to right, most steeply in the lower part, the course of the curves seems to indicate rather convincingly that high protein values in the mother are followed by marked growth in length of the foetus, while low values render lesser growth in length.

In this connection, the agreement between the rapid growth in certain species of animals and the higher protein content of the maternal milk in these species may be recalled (2).

A propos maternal milk, the question may arise whether a comparison with the serum protein values is indicated. In a previous paper (7) it was demonstrated that variations in the serum protein concentration do not co-incide with variations in the tissue protein concentration.

If, in this connection, blood is regarded as an organ of conveyance, it may be conceived without difficulty that the mobilized amount of protein does not necessarily express anything definite concerning the amount stored, in this case the tissue protein concentration. It is possible that an investigation of the variations of the various serum protein fractions might render valuable information. The reader is referred to a paper by Levens (5) who found that the foetal umbilical venous blood is richest in albumin, while the umbilical arterial blood is richest in globulin.

The nature of the conditions towards the termination of pregnancy is unknown and it must also in general be admitted that in this preliminary report information regarding water and fat content is absent.

In Table 1, the tissue protein concentration (percentage of wet weight) in a number of foetal organs is shown. The values show a tendency to increase with increasing age. It should be noted that already in the third lunar month, the liver has reached high values.

From Table 2 it appears that the organs are distributed into certain groups according to the rate of increase of their protein content. It may be presumed that this indicates something of the part played by the various organs in the development of the foetus at various stages: liver and spleen, organs of internal secretion?

The conclusion may be drawn from the results of the present preliminary investigation that it is justified to continue and extend investigations regarding the chemical composition of the human foetus in respect to the chemistry of the individual organs and the interrelationship between the composition of the maternal tissues and the development of the foetus.

Table 2.

Week	% Protein: Maternal fascia	% Protein: Foetal rectus	Foetal length
10.	24.5	8.2	5.5 cm
11.	22.0	5.5	11.0 -
13.	18.7	4.0	10.0 -
»	20.2		13.0 -
»	23.5	11.6	19.0 -
15.	20.2	7.2	15.5 -
»	21.3	6.4	16.0 -
»	21.0	11.0	15.0 -
17.	19.8	8.3	18.0 -
»	22.1	9.8	23.0 -
18.	19.5	8.5	21.0 -
»	20.0	7.6	24.0 -
19.	22.5	8.9	23.0 -
»	21.0	9.5	24.0 -
20.	18.2	8.8	26.0 -
»	20.5	8.4	24.4 -
»	23.5	8.2	27.0 -
21.	21.4	9.6	25.0 -
»	19.3	10.1	22.0 -
24.	19.0	9.0	24.5 -

	IV month		V month
ca. 5—7 %	Cerebrum, Cerebellum, Gl. Thyr., Thymus, Pulmones, Renes, Musculi, Cor	ca. 5—7 %	Cerebrum, Cerebellum, Pancreas, Cor, Pulmones, Intestina
ca. 8 - 10 %	Adrenal gl., Gonads	ca. 8—10 %	Gl. Thyr., Thymus, Adrenal gl., Gonads, Renes, Musculi, Gen. int.
ca. 13—15 %	Hepar, Lien	ca. 13—15 %	Hepar, Lien

SUMMARY

Review of the literature shows that information concerning the chemical composition of the individual organs at various stages of foetal life is not available.

A preliminary orientating investigation concerning 20 human foetuses and their mothers seems to show that the composition of the maternal tissue influences the chemistry of the foetal tissue and foetal growth. High protein concentration in the fascia of the mother's abdominal wall is followed by high protein concentration in the precursor of the rectus abdominis in the foetus and seems to be followed by marked growth in the length of the foetus. The rate at which the various foetal organs attain their highest protein concentration is not identical. Certain groups attain high values first: 1) liver and spleen, 2) organs of internal secretion, — which perhaps indicates something of the significance of these organs for the foetus during the various stages of development.

Research concerning these problems is in progress.

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THE DANISH NATIONAL MORBIDITY SURVEY OF 1950

COMMUNICATION NO. 7. SCOPE AND METHODS

GENERAL REMARKS

A statistical investigation of the general health status of the Danish population was decided in 1950, at the instigation of the National Health Service, it being desired to know what diseases are prevalent among the people, especially those that are not reportable to the health authorities. In addition, information was required as to the part of those ailments for which medical advice is sought. It was also desired to undertake extensive analyses regarding hospitalizations for the purpose of compiling a long-wanted material to show what categories of patients occupy the hospitals, and the circumstances — disease, social status, etc. — that bring about hospitalization. Such an investigation had long been desired by the health authorities as a phase in the combating and prevention of disease, and, thanks to a generous grant from the Rockefeller Foundation, the financial basis was ultimately established for carrying it through.

On account of the composition of her population, her size and her hygienic, social and cultural standards, Denmark offers unusually favourable conditions for making health investigations of this kind.

The first scientific statistical investigation into the *general state of health of an entire group of a population* made by means of direct questioning took place in the United States in the years 1922—24. That investigation was initiated by the Public Health Service and directed by the statistician Sydenstricker, who, in the small town of Hagerstown, for 29 months followed a third of the members of that urban community throughout the entire period. At regular intervals individual persons were asked what ailments they had had within a certain period, the duration of those ailments, their course, etc. In subsequent years the Public Health Service were instrumental in holding a large number of investigations whose principal procedure was the same as the Hagerstown investigation. Under the Ministry of Health in England, a morbidity survey was started in 1943 and continued until the spring of 1952, when the survey was discontinued as part of the British Government's efforts to cut down costs in the Central Administration.

In 1950—51 Canada carried out a morbidity survey for the purpose of ascertaining how much disease there was in the country and also what need there was for medical personnel, hospitals and other health measures; furthermore, what the cost of the Health Services was, in the broadest sense of the term. In California, very thorough pilot studies were made for a morbidity survey comprising the entire state, and the survey itself was started in May, 1954, lasting one year. Investigations of similar character, but less comprehensive, have taken place in Ceylon, in Chile, and in Japan.

On the basis of its statistical material the Danish insurance company "Hånd i Hånd" in 1940 published a book: The Occurrence and Duration of Diseases, by Viggo Kampmann. That work has been the only one of its kind in this country.

After protracted negotiations with the Rockefeller Foundation, the Danish government and various private Danish institutions, it was possible in 1949—50 to secure enough financial assistance to enable a *committee* to be appointed in 1950 to arrange the financing and proper accomplishment of the survey. This committee established a sub-committee to supervise the practical execution of the plan, and the survey was arranged to work over a 3-year period. The investigation methods in England were studied thoroughly, some pilot studies were undertaken, and the work in the field was commenced on June 1st, 1951, and lasted until June 1st, 1954.

Since 1952 the survey has been working under the auspices of the World Health Organization,

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From the Committee on the Morbidity Survey. Chairman *Johs. Frandsen.*

and the Regional Office for Europe has given most valuable assistance in the way of consultants, fellowships and office equipment.

The *cost* of the entire 3-year investigation, including the preparation of the records, was budgeted at D.Crs. 650.000, but it must be observed, in addition, that the technical preparation of the material was undertaken by the State Department of Statistics.

The *final results* of the investigation cannot be analysed thoroughly until all the observations have been assembled and the whole statistical material has been prepared. Before that can be done it is, however, possible to finish preliminary preparations of some of the investigations, and short papers on these subjects will be published separately as soon as they are ready.

There are two parts of the investigation, the morbidity survey and the hospital survey.

I. THE MORBIDITY SURVEY

By MARIE LINDHARDT

As mentioned above, the morbidity survey was carried on over a 3-year period, namely from June 1st, 1951 until June 1st, 1954.

The *method* employed in the morbidity survey was to make a random sample of about 100,000 adults. Each month 3,000 persons were questioned as to their state of health in the previous month, corresponding to 1 per thousand of the total adult population. Each of these selected persons was questioned only once. This was the method employed in England, whereas in the U. S. A. another method has chiefly been used, a certain group of people — families, households — being questioned several times with a certain interval between each interview. The former method has been employed in Denmark because it is expected to give not only the largest, but also the most homogeneous material. In the single-interview system all are equally unprepared to answer the questions, whereas in the follow-up system or the panel system, as it is generally called in English, one runs the risk that during the latter part of the census the respondent will give unnecessarily detailed information compared with the first time he was questioned. A very important point in this method is that the respondent alone must give the replies, and that the interviewer sits in private with the respondent so that he may not be prevented by the presence of others from answering freely and exhaustively to all the questions. Finally, it must be remarked that in Denmark and in England at the time of the surveys there were public registries for the whole of the countries so that one was able to make a correct sampling of the investigation material, whereas there are no similar institutions in the U. S. A.

Before the census work proper was started in June 1951, *pilot studies* were made in Copenhagen and some rural areas. The results of these studies were satisfactory; the people were obliging and valuable corrections for the questionnaire were obtained.

The investigation in the 3-year periods 1951—52, 1952—53 and 1953—54 was held in respectively 208, 201 and 206 *selected communes*, comprising Copenhagen, Frederiksberg and Gentofte, the largest provincial towns with suburbs, as well as a representative section of the metropolitan suburbs, of the other provincial towns and their suburbs, of the built-up rural communes and the "pure" rural communes. Whereas the three metropolitan communes and the largest provincial towns with suburbs were adhered to in all three years, annual changes were made in the representative selection of the other categories of communes.

The selection of communes within each category was made by grouping into strata, each comprising a number of sampling units, of which in most cases three or four in each stratum were selected at random with a probability corresponding to the size of the units. By this means about oneseventh of Denmark's communes were brought into the investigation in each of the three years.

On the assumption that 1/1000th of the adult population of each stratum would be included in the investigation, a calculation based upon the latest population census was made of the fraction of the population in the sampling units which was to be selected every month. In this manner the desired number of interviews for each stratum was distributed equally over the selected sampling units, whereas the interview distribution among communes under the same sampling units was made in proportion to the size of the population.

The *individual persons* were selected with the aid of the public registries which were being carefully instructed as to how the selection was to be made. Each registry was advised as to the fraction of the adult population of the commune to be drawn each time, and, in order to secure the necessary uniformity in the application of the rules, personal visits were made to the public registries in the large towns.

The investigation has employed 165 *interviewers* at any one time in the years 1951—54. The recruitment of these persons was arranged chiefly through the large housewife organizations, but nurses, teachers, social advisers, etc. have also participated in the work. The interviewers were instructed thoroughly as to the purpose of the investigation, the various details of the questionnaire, etc., and the best manner of making contact with the people to be questioned. The latter point is of particular importance, since the successful result of an interview depends greatly upon the interviewer's manner and behaviour.

It having been decided from the start that women may only be questioned by women, never by men, it is more appropriate to employ women who, besides their own sex, can interview men too. This is also the practise in Great Britain, where female interviewers are used exclusively. However, for example in a town such as Copenhagen it may be expedient in certain sections to have male interviewers to question the males; that system has been continued during the whole 3-year period and has given complete satisfaction.

All interviewers signed an undertaking of secrecy, declaring that they were aware of the penalties under the Penal Code for which they would be liable by disclosing what might be confided to them. At the end of each complete interview the interviewer handed the respondent a small printed message: "We thank you", signed by the chairman of the committee. This little leaflet explained briefly the purpose of the investigation. A regular control of the activity of the interviewers was made by means of 7 specially instructed regional supervisors.

The questionnaire was originally drawn up on the model of the English one, but actually it differs a good deal from it in conformity with the different opinions which two separate nations must necessarily hold regarding various matters.

After the necessary preliminaries the interviewer proceeded to ask the person about his health and any sickness in the previous month. As regards what complaints were to be classed as diseases, the detailed instructions given the interviewers verbally and in writing, provided that it must be left to the respondents themselves to decide what they felt was a disease. It might be frequent headaches, sore feet, tired back, and much more of the same kind. If the person declared himself sick with troubles of this nature, they were to be listed as diseases.

The respondent was then asked about the duration of the sickness or ailment, about absence from work, whether he had consulted the doctor or not, any period in hospital, etc. Then came the so-called social part of the questionnaire, where the questions had relation to housing conditions, occupation, employment, etc. Some special questions have been asked in the various years as, for example, concerning dental treatment, smoking habits, the use of sleeping drugs, the use of spectacles, about common colds, about the living conditions of persons of 60 years and over, etc.

The information about the *diseases* was given by and written down by laymen. People themselves are not always aware of the nature of their ailment, and in many cases too they can only give an awkward explanation of what is wrong with them. Consequently, it is a matter of much greater difficulty to apply a classification to such diseases notified by laymen than if the diagnoses had been made by physicians. There is no special list for this purpose and so the following procedure was chosen. A list comprising all these diseases or symptoms was compiled prepared so as to make it as comparable as possible with the International Classification of Diseases drawn up for the first time in 1948. This condensed and modified list comprises about 100 diseases or disease groups as well as accidents.

In order to be more or less able to check the information given, an arrangement was made with the Danish Medical Association, under which doctors who had been consulted by one of the respondents during the investigation month would verify the diseases stated by their patients or correct them if necessary. The physicians have been very ready to collaborate, despite the fact that for a busy practitioner work of this kind increases the burden of returns-writing and certificate-issuing. There was no fee attached to these verifications. By far the greater part of the diagnoses were in perfect agreement with the doctors' opinions of the diseases.

Although this method of investigating morbidity was absolutely new and unknown in the Danish population, it was accepted much better than could be expected. The number of persons who refused to answer the interviewers amounted to only between one and two per cent of the selected persons, exactly corresponding to the English experience.

II. THE HOSPITAL SURVEY

By RICHARD FRIEDBERG

Denmark, with an area of 43,000 sq. km. and a population of 4.3 millions, has about 4,500 doctors and surgeons, of whom over 2,000 are private practitioners and about 2,000 are engaged at the country's curative institutions.

Each of the medico-surgical hospitals, which annually admit over 450,000 patients, compiles an obligatory annual report covering the patients, their diseases and certain administrative details. This reporting duty is more than 75 years old, and although the reports to the National Health Service in time have become more comprehensive in details, they nevertheless provide but a rather one-sided and summary impression of the patients and their diseases and of the hospital administration. For this reason many of the hospitals have taken it upon themselves to draw up more comprehensive reports, but these too are somewhat summary and all suffer from the fundamental defect that from them it is impracticable to correlate the various relevant characteristics of the patients, for example diagnoses, bed-days, examinations, treatment, social conditions and the like.

In order to make these matters more perspicuous the committee arranged a "hospital

survey", which was made in the period from autumn, 1952 to the end of 1953. This survey has made it possible to correlate a large quantity of different individual data in many ways and ought to permit of providing an important supplement to the obligatory hospital report. The material procured through the survey will be useful to both medical men and administrators for scientific as well as purely practical purposes, and, *inter alia*, will be of help to the financing and administrative authorities in the drawing up of rational plans for the hospital system of the future.

At the outset it was obvious that the committee would be unable to undertake a survey comprising all 150 general hospitals with all the 450,000 patients admitted there in a twelve-month period. The task would be insuperable and too heterogeneous. The survey was therefore limited to public hospitals, and of these only those treating patients with medical and surgical diseases proper. This meant the exclusion of hospitals and special departments for patients with, e. g., psychiatric diseases, epidemic diseases, diseases of the ear, nose and throat, eye diseases and others. Children were also ruled out, and thus the survey was confined to persons of 15 years and over.

This selected group of adult patients with medical and surgical diseases comprises about 250,000 patients, i. e., more than half of the total number annually admitted to hospital in Denmark.

Of the 180 departments and hospitals treating patients with medical and surgical diseases, a selection was made of 39 departments and hospitals in the provinces representing about one quarter of the total number of these department categories and 16 departments in the metropolitan area. As it was impracticable for either the Survey Committee or the hospitals in their daily work to have the survey running for a whole year in these departments, a survey period of four months was fixed for departments in the provinces and about five weeks in the metropolitan area.

In the course of these periods information was collected regarding a total of about 27,000 patients, i. e., a good 10 per cent of the total number of patients in medico-surgical departments admitted to hospital in Denmark per annum which was considered a sufficient sample for the purpose of the survey.

The 39 hospitals in the provinces were selected representatively in such a manner that they were evenly distributed over the whole country, with a plurality of hospitals or departments within each geographical area. By this means, various institutions within each of the areas could be brought into the survey at different times of the year, thus eliminating differences that were conditioned geographically or seasonally. Within the metropolitan area the geographical factors are of minor importance, and therefore as many as possible of the municipal hospital departments were brought in at different times of the year.

All in all, the survey comprised about 22,000 adult patients in the provinces and about 5,000 in the metropolitan area.

The survey material was collected through the medium of a questionnaire for each patient. It contains about 50 questions, covering the patient's marital status, diagnosis, treatment, examinations, etc. Thirty of the questions were answered by the hospital doctors and nurses, and the committee's own staff answered the remaining 20 from the case records.

The majority of the questions were provided with a code number (precoded), whereby for purposes of analysis the data on the questionnaire could be transferred direct to punched cards. This does not apply to the diagnoses, which were coded later by the committee staff on the basis of the 3-digit list in the International classification of Diseases and Causes of Death.

Before the survey started, pilot studies were made in order to ascertain the extent to which the hospital departments would be burdened by the survey. These tests having proved that the daily work of the departments did not suffer, a start was made with building up understanding and goodwill for the survey by means of articles in the journals of the medical and nursing professions and by personal approach to the heads of those departments which had been selected to take part.

In the provinces the survey was initiated after talks between a doctor sent out by the committee and the hospital staff. Both verbally and in writing this doctor instructed the medical men and the nurses who were to help in the survey and made arrangements with one of the hospital physicians for the daily supervision; finally, the survey period was fixed. Five or six weeks after this instruction and the commencement of the survey the committee sent a travelling team to the hospitals. The team comprised a doctor, a statistician and a clerk, and its object was to inspect the part of the survey so far completed, to advise in questions of doubt and to answer the part of the questionnaire that was not to be filled in by the hospital's own doctors and nurses.

While the clerk was busy at the hospitals already embarked on the survey, the doctor went on to instruct those next in turn.

Finally, the team made another visit about two months after the end of the survey period and continued with the answers to the questions to be answered by the team itself from the hospital case records. All the questionnaires sent to the department were then collected, 22,000 in all. As a matter of interest it may be added that the team made a total of nine rounds of inspection, covering a total of four months travelling about 15,000 km by motor-car alone.

In the metropolitan area the survey proceeded on practically the same lines, except that the short distances made it possible to collect the 5000 questionnaires gradually as the patients concerned were discharged from the 16 hospital departments.

In addition to securing actual data, it was desired to make comparisons between the hospital system, occupancy, etc. of to-day with conditions earlier; a collection was therefore made at some of the departments in the survey of certain particulars concerning a total of about 5,000 patients based upon a case-record material 25 years old. From this, of course, it was impossible to extract as much information and in such detail as in the hospital survey itself, but the material assembled is considered to be suitable for some comparison.

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MEDICO-STATISTICAL INFORMATION FROM DENMARK FOR THE YEARS 1953 AND 1954

By KAREN DREYER and HENRY HAMTOFT

Table 1.

Population:
Census, November 7th, 1950: 4,281,275.
Estimated, July 1st, 1954: 4,405,700.

Live-born	1953	78,261 = 17.9	per 1,000 population
	1954	76,437 = 17.4	per 1,000 population
Still-born	1953	1,543 = 1.9	per cent of total births
	1954	1,505 = 1.9	per cent of total births
Deaths total	1953	39,350 = 9.0	per 1,000 population
	1954	39,885 = 9.1	per 1,000 population
Deaths under 1 year	1953	2,130 = 27.2	per 1,000 live-born
	1954	2,051 = 26.8	per 1,000 live-born
Notifiable diseases [1]	1953	841,031 = 192	per 1,000 population
	1954	902,761 = 205	per 1,000 population

[1]) Except venereal diseases, delirium tremens and scabies.

December 31st 1953.

Practising physicians: 4,750 = 1 per 920 inhabitants.
Practising dentists (total): 2,140 = 1 per 2,041 inhabitants.
Dentists with own practice: 1,299 = 1 per 3,364 inhabitants.
Pharmacies: 349 = 1 per 12,624 inhabitants.
Practising midwives: 759 = 1 per 1,401 women in the age group 15—64 years.
Number of active members of Council of Danish Nurses: 13,200.

From the National Health Service.

The information in Table 1, together with that of Table 2, showing the number of reported cases of epidemic diseases, indicate that the epidemic morbidity in the years 1954 and 1953 remained on the same high level as in 1950 and 1952 where 197 cases per 1,000 population were notified. During the whole quinquennial period 1949—53 there were notified on an average 184 cases per 1,000 population per year. The largest numerical increase from 1953 to 1954 occurred for measles, tonsillitis and acute pulmonary diseases while the greatest decrease occurred for influenza and poliomyelitis. Diphtheria was notified with 7 cases in 1954, but the diagnosis was verified only in one case.

The number of reported cases of gonorrhoea has been increasing since 1952 while the number of syphilis cases continued a downward trend since 1945. The increasing number of cases of gonorrhoea does not necessarily mean a greater number of patients, since the possibility of getting this disease more than once during a year has increased since the introduction of penicillin-treatment.

Table 3 shows the distribution of the notified cases by age and it may be seen from the table that the epidemic morbidity has increased for all age-groups compared with the quinquennial period 1949—53.

Table 2.
The epidemic morbidity in Denmark 1954 and 1949—53.

	Reported cases		per 10,000 pop.	
	1954	1949—53	1954	1949—53
Typhoid fever	31	20	0,1	0,0
Paratyphoid fever	64	48	0,1	0,1
Epidemic cerebrospinal meningitis	136	138	0,3	0,3
Acute anterior poliomyelitis, total	352	1909	0,8	4,4
—, paralytic	72	725	0,2	1,7
Epidemic cerebrospinal meningitis	24	14	0,1	0,0
Dysentery	252	270	0,6	0,6
Intermittent fever, originating in Denmark	—	—	—	—
—, outside Denmark	11	12	0,0	0,0
Diphtheria	1	34	0,0	0,1
Scarlet fever	4536	5212	10,3	12,1
Puerperal fever	29	58	3,8[2])	7,4[2])
Pemphigus neonatorum[1])	267	245	34,9[3])	31,4[3])
Tetanus neonatorum[1])	11	32	1,4[3])	4,1[3])
Measles	61110	42998	138,7	99,9
German measles	24715	9448	56,1	22,0
Chicken-pox	24607	22489	55,9	52,3
Whooping-cough	41671	49279	94,6	114,5
Mumps	18935	18212	43,0	42,3
Influenza	256371	210912	581,9	490,1
Angina and tonsillitis	197747	180157	448,9	418,6
Tracheo-bronchitis	143343	138948	325,4	322,9
Bronchopneumonia	58477	48042	132,7	111,6
Lobar pneumonia	6283	6337	14,3	14,7
Cholerine and enteritis	53866	47429	122,3	110,2
Epidemic hepatitis	4539	6035	10,3	14,0
Rheumatic fever	1484	1940	3,4	4,5
Erysipelas	3899	4127	8,8	9,6
Gonorrhoea, not previously diagnosed	8215	8263	18,7	19,2
Soft chancre, not previously diagnosed	14	21	0,0	0,0
Acquired syphilis, not previously diagnosed	114	521	0,3	1,2
Congenital syphilis, not previously diagnosed	10	18	0,0	0,0
Lymphogranuloma inguinale	7	6	0,0	0,0
Delirium tremens	25	23	0,1	0,1
Scabies	6653	11914	15,1	27,7

[1]) Under 1 month
[2]) per 10,000 parturients
[3]) per 10,000 live-born

Table 3.
Notifiable diseases according to age 1954 and 1949—53.

Age	Cases	per 1,000 population	
		1954	1949-53
0— 1 year	49948	649	588
1— 4 years	196946	653	541
5—14 »	237898	300	274
15—64 » males	176396	127	116
15—64 » females	180953	127	116
65 years and o. males	30126	151	127
65 years and over females	30494	136	115
Total	902761	205	184

The crude mortality rate was nearly the same in 1954 and 1953, namely 9.1 per 1,000 against 9.0 in 1953 and 1952. From 1953 to 1954 there was a decline in the number of deaths in all age groups below 45 years which, however, was more than outweighed by the rise for the age groups over 65, resulting in a total increase of 535 deaths.

The infant mortality has remained nearly constant in 1954, 26.8 per 1,000 live-born, as against 27.2 in 1953.

Table 4.
Deaths per 1,000 population by age and sex 1921 and 1954.

	1921		1954	
	M.	F.	M.	F.
Under 1 year	87.9	67.2	30.9	22.0
1— 4 years	5.6	4.4	1.4	1.1
5—14 »	1.7	1.7	0.4	0.3
15—24 »	2.9	2.7	1.1	0.4
25—34 »	3.5	3.7	1.3	1.0
35—44 »	4.4	5.4	2.3	1.9
45—54 »	8.7	8.6	6.0	4.7
55—64 »	18.2	17.1	15.3	11.0
65 years and over	70.4	70.8	64.3	59.9
Total	11.2	11.2	9.4	8.7

Table 4 shows the mortality by age and sex. The figures show that the decline from 1921—54 has been much heavier in the younger age-groups than among the older part of the population. Furthermore, it is seen that females show a greater decrease in mortality than males. The former excess mortality of women in the age groups 25—44 has now disappeared.

Table 5.
Causes of Death in Denmark 1954 and 1953.
Abbreviated List (B).

			Total		per 100,000 pop.	
			1954	1953	1954	1953
B	1	Tuberculosis of respiratory system	310	341	7.0	7.8
B	2	Tuberculosis, other forms	31	44	0.7	1.0
B	3	Syphilis and its sequelae	92	110	2.1	2.5
B	4	Typhoid fever	—	1	—	0.0
B	6	Dysentery, all forms	3	1	0.1	0.0
B	7	Scarlet fever and streptococcal sore throat	2	—	0.0	—
B	8	Diphtheria	—	1	—	0.0
B	9	Whooping cough	16	28	0.4	0.6
B	10	Meningococcal infections	7	10	0.2	0.2
B	12	Acute poliomyelitis	4	86	0.1	2.0
B	14	Measles	10	19	0.2	0.4
B	17	All other diseases classified as inf. and parasit.	159	166	3.6	3.8
B	18	Malign. neoplasms, incl. neoplasms of lymph. and hæmatopoetic tissues	8370	8114	190.0	185.7
B	19	Benign and unspecified neoplasms	374	374	8.5	8.6
B	20	Diabetes mellitus	262	222	5.9	5.1
B	21	Anæmias	105	109	2.4	2.5
B	22	Vasc. lesions affect. central nervous system	5376	5532	122.0	126.6
B	23	Nonmeningococcal meningitis	40	64	0.9	1.5
B	24	Rheumatic fever	15	16	0.3	0.4
B	25	Chronic rheumatic heart disease	317	293	7.2	6.7
B	26	Arteriosclerotic and degenerative heart disease	8908	8301	202.0	190.0
B	27	Other diseases of heart	1552	1442	35.2	33.0
B	28	Hypertension with heart disease	944	1042	21.4	23.8
B	29	Hypertension without mention of heart	169	190	3.8	4.3
B	30	Influenza	397	331	9.0	7.6
B	31	Pneumonia	969	958	22.0	21.9
B	32	Bronchitis	272	162	6.2	3.7
B	33	Ulcer of stomach and duodenum	307	306	7.0	7.0
B	34	Appendicitis	125	135	2.8	3.1
B	35	Intestinal obstruction and hernia	294	286	6.7	6.5
B	36	Gastritis, duodenitis, enteritis and colitis, except diarrhoea of the newborn	183	200	4.2	4.6
B	37	Cirrhosis of liver	306	254	6.9	5.8
B	38	Nephritis and nephrosis	270	327	6.1	7.5
B	39	Hyperplasia of prostate	554	604	12.6	13.8
B	40	Complications of pregnancy, childbirth and the puerperium	52	65	1.2	1.5
B	41	Congenital malformations	417	466	9.5	10.7
B	42	Birth injuries, postnatal asphyxia and atelectasis	520	519	11.8	11.9
B	43	Infections of the newborn	35	22	0.8	0.5
B	44	Other diseases peculiar to early infancy, and immaturity unqualified	613	647	13.9	14.8
B	45	Senility without mention of psychosis, ill-defined and unknown causes	672	747	15.3	17.1
B	46	All other diseases	3857	3882	87.6	88.9
BN	47	Fractures, head injuries and internal injuries	1525	1463	34.6	33.5
BN	48	Burns	53	48	1.2	1.1
BN	49	Effects of poisons	731	690	16.6	15.8
BN	50	All other injuries	667	732	15.1	16.8
		Total	39885	39350	905.3	900.6
		Alternative classification of deaths from accidents, poisonings and violence (BN 47 — BN 50) according to external cause:				
BE	47	Motor vehicle accidents	666	521	15.1	11.9
BE	48	All other accidents	1249	1301	28.4	29.9
BE	49	Suicide and self-inflicted injury	1028	1054	23.3	24.1
BE	50	Homicide and operations of war	33	57	0.8	1.3

Since 1951 The International Statistical Classification of Diseases, Injuries, and Causes of Death of 1948 has been applied to the Danish causes of death tabulation. Table 5 shows the causes of death in 1954 and 1953 according to the Abbreviated List. Tuberculosis deaths have reached a new minimum, the rates per 100,000 population in 1954 being 7.0 and 7.7 for respiratory and all tuberculosis respectively, whereas cancer shows the highest rates ever reached in this country, namely 186 and 190 per 100,000 in 1953 and 1954 respectively.

Table 6.
Percentage distribution of major causes of death 1921 and 1954.

	1954	1921
Accidents, poisoning and violence....	7	3
Cancer	21	12
Heart diseases	27	10
Vascular lesions affecting central nervous system	13	5
Tuberculosis	1	9
Other infectious diseases.....	1	7
All other causes of death	30	54
Total..	100	100

A division of violent deaths into traffic accidents, other accidents, suicide and homicide shows that in 1954 one half to one third of all these deaths in the younger age groups (under 25 years) was caused by traffic accidents, whereas suicide is a predominant cause of violent death in the age groups between 25 and 65 years, close to one half of the violent deaths among males, and far more than one half among females being attributed to suicide.

The percentage distribution of causes of death in 1954 and 1921 in some broad groups was as indicated in Table 6.

This comparison shows, as could be expected, that tuberculosis and other infectious diseases now play a minor role as causes of death, whereas cancer and heart diseases make up altogether approximately one half of all deaths. The first 6 groups, mentioned here, are altogether responsible for almost 70 per cent of all deaths in 1954, but only 46 per cent in 1921, the rise within the first four groups by far outweighing the decline in the infectious diseases. However, it should be emphasized that the increase of deaths caused by cancer, heart diseases and vascular lesions affecting central nervous system are due to not only a real increase of these diseases, but also to the rise in the number of aged, and to the change of the classification systems applied.

The fight against tuberculosis, as mentioned above, has resulted in new low death rates for this disease in 1953 and 1954. Also the number of notified cases is on a downward trend, 1,764 cases of pulmonary tuberculosis or 40 per 100,000 population being recorded in 1953, as against 2,060 or 48 per 100,000 in 1952. The rate is, as has been the case since 1942, lower for females than for males. It must be mentioned that all cases notified by physicians are accepted regardless of whether the diagnosis is based on demonstration of tubercle-bacilli or on clinical symptoms only. 82 per cent of all cases were bacillary cases, however. The number of notified cases of extrapulmonary tuberculosis in 1953 was 219 or 5 per 100,000 population. At the end of 1953 there were altogether 14,939 known cases of pulmonary tuberculosis in Denmark or 342 per 100,000 population. The corresponding figures for extrapulmonary tuberculosis were 1,328 and 30 respectively. The cases were distributed according to age and sex as shown in table 7.

Table 7.
Known cases of tuberculosis by age and sex, December 31st, 1953.

	Respiratory tuberculosis		Extrapulmonary tuberculosis only	
	Males	Females	Males	Females
0— 4 years	141	107	2	4
5—14 »	564	491	40	20
15—24 »	770	1159	53	56
25—44 »	3454	4251	305	323
45—64 »	1935	1235	185	213
65 years and over	478	354	47	80
Total..	7342	7597	632	696

There are 102 chest clinics in Denmark including one central clinic in each county. The chief physician at the central clinics is also chief physician of the local tuberculosis hospital. In 1953 these clinics gave altogether 1,380,000 consultations and performed 317,000 tuberculin tests. 166,000 persons were referred for examination and 50,000 BCG-vaccinations were made. In all 1,300,000 persons in Denmark are vaccinated now besides those vaccinated in schools.

The number of examinations according to the Act concerning Pregnancy Hygiene was 174,000 at the doctors and 287,000 at the midwives in 1953/54. Table 8 shows the use of this act. The percentage of utilization was much higher in towns, partly due to the fact that many women from the rural districts visit doctors in towns.

The number of public health nurses visiting infants has increased from 320 in 1953 to 331 in 1954. 158 of these nurses were at the same time school health nurses. The school health service employed in addition 54 specially trained public health nurses and 202 other nurses. 46,537 children, i. e., 60 per cent of all live-born, were under supervision of these visiting nurses against 58 per cent in 1953. The nurses made 862,000 visits and 17,800 references to a doctor.

365,000 examinations by physicians of children below 7 years were made last year against 363,000 2 years before. This means that 53 per cent of all possible examinations were really made against 51 per cent the year before.

67 municipalities arranged in 1953/54 school-meals for 200,000 school-children. In the capital 95 per cent of all children, who were offered school-meals, participated, against 65 per cent outside the capital.

School dentist services are now introduced in the capital, all cities and in 481 of in all 1,305 rural municipalities.

Since 1806 the general hospitals of Denmark have been the responsibility of the local authorities, the counties and the cities, while the number of private hospitals is insignificant in relation to the aggregate hospital system.

Table 8.
Number of visits to physicians and midwives according to Act concerning Pregnancy Hygiene.

	Whole country	Fiscal year	April 1st – March 31st.	
	1946/47	1946/50 average	1952/53	1953/54
1st visit to physician	71990	69622	71188	71123
Utilization (i.e. 1st visit in per cent of live born children)	83[1] 65[2]	90[1] 72[2]	105[1] 83[2]	102[1] 83[2]
2nd and 3rd visit to physician	90019	95033	100669	102592
Utilization (i.e. 2nd and 3rd visit in per cent of 1st visit)	71[1] 54[2]	72[1] 64[2]	72[1] 70[2]	73[1] 71[2]
Visits to midwives (maximum 7)	260533	266581	286182	286587
Utilization (i.e. visits to midwives in per cent of 1st visit to physicians)	62[1] 41[2]	63[1] 47[2]	63[1] 52[2]	64[1] 52[2]
Number of live born children in calendar year	96100	87140	76900	78300

[1]) Towns [2]) Rural districts.

Table 9.
Beds in hospitals and other institutions for treatment of the sick. December 31, 1953.

	No. of institutions.	No. of departments	No. of beds total	No. of beds per 1,000 population
1. Hospitals:				
Hospitals with special departments	67*)	222*)	19061	4.36
Hospitals mostly with mixed departments	81	86	6328	1.45
viz. mixed departments		(81)	(6215)	(1.42)
viz. special departments		(5)	(113)	(0.03)
All hospitals	148	308	25389	5.81
2. Other institutions:				
Infirmaries in old-age homes, etc.	50	...	2959	0.68
Private clinics	20	...	425	0.10
Municipal maternity hospitals	3	...	109	0.02
Nursing institutions	43	...	2792	0.64
Tuberculosis hospitals	38	...	2782	0.64
Mental hospitals	10	...	9408[1])	2.15
Epidemic hospitals	3	...	931	0.21
Total	...	...	19406	4.44
All hospitals and institutions	...	...	44795	10.25
In addition accommodation in:				
Asylums for feeble-minded	4	...	6926[2])	1.59
Institutions for the blind	9	...	434	0.10
Institutions for deaf-mutes	8	...	606	0.14

See table 10 concerning activity of special departments.
[1]) In addition accommodation for 1042 patients in family nursing.
[2]) In addition accommodation for 7175 patients in family nursing.

A reorganization of the hospital system has been proceeding since about 1930, aiming at establishing in every county one or two so-called "Central Hospitals" with a surgical, a medical and a radiological department as a nucleus. Other special departments may be and have in many cases already been added. The purpose of this reorganization was to ensure the whole population, rural as well as urban, a share in the great progress of medical science, and the development has been so rapid that there is now at least one Central Hospital in every county.

Table 9 gives a survey of the number of beds in hospitals and other institutions according to the type of institution.

Table 10 shows the number of special departments with figures for beds and patients for the whole country, and the length of stay per patient, counting only hospitalized patients, the criterion of a special department being that it is in the charge of a specialized physician, regardless of its size.

The year 1945 was the first for which the hospitals made standard returns of the diseases

Table 10.
Number of beds, admissions and average length of stay in special departments in Danish hospitals 1953.

Departments	No. of departments	No. of beds	Admissions	Average length of stay, days
Medical	53	6244	95,063	22
Surgical	48	5793	149,101	15
Neurological	6	456	7,976	22
Brain-surgical	3	144	3,868	13
Orthopaedic	6	423	6,453	25
Gynaecological	11	705	19,290	13
Maternal	5	387	9,527	12
Otolaryngological	24	706	19,057	11
Ophthalmological	19	314	5,667	16
Paediatric	11	855	10,173	26
Dermato-venereal	7	491	6,417	25
Radium	3	302	4,352	25
Fysiurgic	1	42	458	37
Epidemic	5	737	9,193	22
Psychiatric	4	506	11,013	19
Tuberculosis	21	1069	4,507	73
Total 1953	227	19174	362,115	
Total 1952	225	19151	352,815	

treated during the year. The basis of these returns is the National Health Service's list of diagnoses. In Table 11 is shown the result of a compilation of the statistics for the whole country. It is clearly realized that this list is far from ideal, and work is going on, aiming at establishing a list based on The International Statistical Classification of Diseases, Injuries, and Causes of Death of 1948.

As will be seen, the total number of patients has been increasing and is now 112 per 1,000 inhabitants against 105 in 1949 and 107 in 1945.

Great changes have taken place during the last years regarding the frequency of different diseases. Some groups are much more frequent now than before, e. g., digestive diseases, diseases of the circulatory system, gynaecological diseases, nervous diseases, tumours and traumatic injuries. There are fewer cases now of skin diseases and infectious diseases including venereal diseases. The total number of patients for these two last mentioned groups has fallen from 75,000 in 1945 to 34,000 in 1953. This decline alone has made it possible for the hospitals to treat roughly 40,000 patients more for other diseases. The total number of patients in the general hospitals was 484,330 patients with a total number of 8.8 million sick-days. The average number of patients of the 25,400 beds was 24,100, showing that the beds were used to a degree of 95 per cent.

Every year the National Health Service draws up a survey of the working expenses of public hospitals, based upon returns sent in by the hospitals on specially designed forms. The information in Table 12 is taken from the last financial year for which all the figures are available.

The average outlay per patient-day for the whole country in 1952/53 was 35.85 Danish Crowns. Per board-day the expense was 2.36 D. Crs. The expense per head of population was

Table 11.
Survey of Cases admitted to Danish General Hospitals. 1953—1949—1945.

	Main diagnoses			per 1000 diagnoses		
	1953	1949	1945	1953	1949	1945
1. Respiratory diseases	22,578	23,450	21,761	46.0	52.7	50.7
2. Senile diseases	804	717	538	1.6	1.6	1.3
3. Diseases of musculo-skelet. system	22,231	19,395	19,198	45.3	43.5	44.7
4. Diseases of the blood and blood-forming organs	3,387	2,958	2,143	6.9	6.6	5.0
5. Endocrine diseases	13,687	11,610	10,212	27.9	26.1	23.8
6. Diseases of the digestive system	80,845	69,203	61,848	164.8	155.4	144.0
7.a Poisonings, acute	4,953	3,769	3,782	10.1	8.5	8.8
7.b Poisonings, chronic	1,249	1,028	369	2.5	2.3	0.9
8. Skin diseases	14,088	16,978	27,797	28.7	38.1	64.7
9. Infectious diseases*)	20,113	30,441	47,603	41.0	68.3	110.8
10. Diseases of the circulatory system	29,537	22,949	15,497	60.2	51.5	36.0
11a. Diseases of the genitals, male (excl. venerea)	6,111	5,662	4,441	12.5	12.7	10.3
11b. Diseases of the genitals, female (excl. venerea)	34,040	28,078	23,679	69.4	63.0	55.1
12. Malformations, congenital	2,614	2,331	1,944	5.3	5.2	4.5
13. Organic diseases of the nervous system	14,739	12,900	9,927	30.1	29.0	23.1
14. Functional diseases of the nervous system	22,942	20,841	17,734	46.8	46.8	41.3
15. Infantile diseases	2,593	2,990	3,140	5.3	6.7	7.3
16. Diseases of the urinary system	12,655	9,744	8,924	25.8	21.9	20.7
17. Diseases of pregnancy and childbirth	29,055	23,520	25,250	59.2	52.8	58.8
18. Normal pregnancy and birth	47,126	44,703	42,259	96.1	100.4	98.4
19a. Tumours, malignant	17,274	14,722	12,272	35.2	33.1	28.6
19b. Tumours, benign	12,445	9,091	8,030	25.4	20.4	18.7
20. Traumatic injuries	43,957	35,660	31,432	89.6	80.1	73.2
21. Eye diseases	6,568	6,311	5,823	13.4	14.2	13.6
22. Ear diseases	8,179	11,718	9,711	16.7	26.3	22.6
23. Observations and other uncertain cases	16,677	14,606	14,243	34.0	32.8	33.1
Total	490,447	445,375	429,557	1000.0	1000.0	1000.0
per 1,000 population	112	105	107			
*) hereof venereal diseases	870	1,884	9,085	1.8	4.2	21.1

Table 12.
Working expenses of all public hospitals 1952/53. In Danish crowns (1 D. Cr. = 1 sh = 0,14 U.S.$).

	Total	In per cent of total: Wages	Board	Other expenses
	1,000,000 D. cr.			
County and municipal hospitals	251.8	55.6	10.4	34.0
State hospitals	29.7	60.7	7.7	31.6
Total 1952/53	281.5	56.2	10.1	33.7
Total 1951/52	254.3	54.0	10.8	35.2

64.42 D.Crs. The rise in the expenses for hospitals is mainly due to the rise in wages.

All institutions for the treatment of sick people employed 1981 physicians (of which 492 chief physicians) and 9,500 registered nurses.

CELLULAR AMINO ACID METABOLISM

SUMMARY OF THESIS

By JØRGEN KIELER

As part of a series of investigations aiming at the elucidation of possible differences in the amino acid requirements of normal and malignant cells in tissue cultures, the effect of various amino acids on the mitotic activity of embryonic chicken heart fibroblasts *in vitro* was examined.

Preliminary experiments showed that the stimulatory effect of the nutritional medium on cell division is reduced by dialysis to such an extent that the promoting effect of low molecular weight substances added to dialyzed material can be demonstrated. Furthermore, such a material will be suitable as basic medium in the study of the nutritional value of its dialyzable components, since evidence was obtained that the inhibiting influence of dialysis on mitosis is due to the elimination of low molecular weight substances and not to denaturation of the non-dialyzable fraction of the medium.

The mitotic activity in cultures grown in dialyzed material could be partially restored by adding a solution of nine amino acids in the same relative concentrations as in hydrolyzed fibrin — the so-called Bergmann mixture. Maximal effect was obtained at a total amino acid nitrogen concentration of 5 mg per cent, at which concentration the mitotic activity rose from 17 to 60 per cent of control values from cultures grown in a non-dialyzed medium.

Further improvement was observed, when the concentration of one of the diamino acids (arginine, lysine and histidine) or one of the dicarboxylic amino acids (glutamic acid and aspartic acid) was increased. The presence of methionine and tryptophane was essential for the effect of Bergmann's solution, while proline and cystine were found to be without any stimulating influence on the mitotic activity.

The effect of the individual amino acids was found in several cases to depend on the simultaneous concentration of other amino acids. Thus, lysine at a concentration of 25 mg per cent had a stimulatory effect on mitosis if histidine was present in the medium. However, in the absence of the latter amino acid, lysine had a pronounced cytotoxic effect at this concentration. Similar relations were demonstrated between arginine and histidine, and between arginine and lysine. Glutamic acid was completely able to replace aspartic acid, but could only be partially replaced by the latter amino acid. In addition, aspartic acid inhibited to some extent the stimulatory influence of glutamic acid on mitosis while, on the other hand, glutamic acid neutralized the partial metaphase arrest caused by aspartic acid. The effect of tryptophane also seems to depend on the simultaneous concentration of other amino acids. The tryptophane requirement of the cells increased when the concentration of the diamino acids, the dicarboxylic amino acid, and methionine were raised.

Differential counting of the mitotic phases showed that lysine deficiency was followed by retardation of prophase, while arginine deficiency had the opposite effect. In addition to stimulation of mitosis, aspartic acid caused a partial arrest of metaphase. In non-toxic concentrations the remaining amino acids were without any clear influence on phase distribution.

Cells grown in a dialyzed medium showed various signs of degeneration, such as cytoplasmic deterioration, accumulation of sudanophilic vacuoles, displaced and broken chromosomes and pyknosis. Improvement of signs of cytoplasmic degeneration was particularly obtained by the addition of glutamic acid, arginine, lysine and methionine, while chromosomal abnormalities disappeared or became less conspicuous, when tryptophane, glutamic acid, lysine and methionine were present in the medium.

From these experiments it is not possible to draw final conclusions regarding the way of action of the individual amino acids on mitosis. However, the above-mentioned results are discussed on the basis of a survey of the synthetic processes which are known or supposed to be involved in the production of nuclear substances.

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A NEW DRUG EFFECTIVE ON THE CENTRAL NERVOUS SYSTEM

During recent years, some new compounds have been brought into use in the treatment of psychoneurosis; first chlorpromazine, and reserpine; later more have been added, and as seen in this issue of the Danish Medical Bulletin, a new Danish product has also been brought under clinical trial. Benactyzine (NFN)*) differs in many respects from the other types of drugs brought into use in neuroses. The compound has been known since 1936 (1) and its peripheral effects are comparatively well known. It is a spasmolytic; the anticholinergic effect is about 25 % of atropine (2, 3, 4, 5) and especially the mydriatic effect is pronounced (2, 6, 7, 4). The anti-Ba++ effect is about 50 % of papaverine (2, 3, 4, 5). Moreover, it is a local anaesthetic (3, 8) and has a quinidine-like effect on the heart 3 times as strong as quinidine itself (9). However, these peripheral effects have never been utilized clinically except for the mydriatic effect, where a solution for topical use has been marketed (10).

The toxicity is low, (LD_{50} in rodents is about 100 mg/kg i. p.). The toxic symptoms in animals are few and uncharacteristic, first appearing after administration of 75 % of the average lethal dose (5). In normal human subjects, doses of 4—6 mg have very pronounced effects: dizziness, ataxia and a feeling of relaxation of the striated muscles. A subjective feeling of a blocking of the spontaneous thought stream, "a maximal absent-mindedness", is very striking. Hallucinations or confusion are never seen, even after high doses (5, 11). After moderate doses, only a slight or even no decrease of the mental functions is found in psycho-technical tests (12). Objectively, the α-waves of the EEG disappear during the height of the subjective symptoms after 4—6 mg subcutaneously (13).

Small doses of Benactyzine potentiates the anaesthetic effect of Evipan (hexobarbital), a few other barbiturates, and alcohol in mice, and abolishes the Hermann-Straub tail-raising reaction after morphine.

In doses giving no or few objective and subjective effects Benactyzine has a clear influence on the reaction in different stress situations. The behaviour of rats expecting a mild electric shock in the Gellhorn cage is normalized after doses of 1—4 mg/kg s. c. At the same time the conditioned responses are more frequent and coordinated (14). The conflict-induced behaviour of cats in experiments with the Masserman technique is also normalized after about 0.2 mg/kg s. c. (15). In man daily doses of 0.07 mg/kg perorally during one week were able to diminish or abolish the autonomic reactions after induced, graduated emotions (16).

The experiments in rats, cats and man indicate that Benactyzine in doses giving practically no other symptoms is able to increase the emotional threshold for external influences. This effect together with the blocking of the thoughts, which also involves rumination, gives a strong indication for its usefulness in the treatment of psychoneurotics. Preliminary clinical experiments by Munkvad (17) and the more detailed analysis by Østergaard Jensen (18) and Ostenfeld (19) have confirmed this assumption. A rough estimate indicates that Benactyzine is able to add further 50 % to the present therapeutic results in psychoneuroses with anxiety, asthenic, depressive, or obsessive-compulsive reactions. Psychoneuroses with hysterical reaction seem to be unaffected or perhaps even worsened. No effect is seen on endogenous depressions.

The side-effects of Benactyzine are slight and seem only to be due to the atropine-like effect of the drug. Of special importances is that no indication of an addiction to the drug has been noted in the about 600 patients hitherto treated. On the contrary, not a few patients have spontaneously stopped the medication when they felt better.

The mentioned properties of Benactyzine, the thought-blocking effect, and the increase of the emotional threshold supports the self-limiting tendencies of psychoneuroses in the optimal cases, psycho-therapy is facilitated and the patients get a better insight in their problems. As also stated with some other new remedies, it takes some time (a few days to some weeks) until an effect is seen. This opens interesting theoretical perspectives. In psychoneuroses, apparently some vicious circulating processes within neuron chains in the central nervous system must be broken and new more healthy pathways opened, before an improvement is seen.

Benactyzine seems to work on a level in the central nervous system different from the other drugs used in psychoneurosis. It does not induce sleep as the barbiturates. It has no effect on the metabolism and body temperature as does chlorpromazine (5). It has no effect on the normal or pathological blood pressure as reserpine. Chlorpromazine has not the described effect on the stress-induced behaviour in rats and cats (10), and reserpine only to a slight degree. Unlike reserpine, Benactyzine has no effect on the aggressive tendencies in monkeys, and also in man it mainly seems to work on the effect of conflicts rather than on aggression. Many drugs derived from antihistamines have a depressing effect on the spontaneous activity of rats; this is not seen with Benactyzine (5). Finally, neither reserpine, chlorpromazine, nor other compounds derived

*) Benactyzine (NFN) is the proposed generic name, accepted by the Scandinavian Pharmacopoeia Commission (NFN). Registered names in different countries are Suavitil ® or Parasan ®. Chemically it is the hydrochloride of benzilic acid diethylaminoethylester.

from the antihistaminics have a specific effect on the EEG.

The perspective of possessing a full register of different drugs, acting on different levels of the central nervous system, opens wide possibilities for the pharmaco-therapy of mental diseases. It is to be hoped that the new Danish product may offer a contribution to this important field of the medical science.

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